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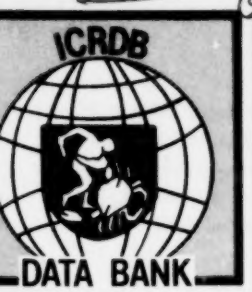

ONCOLOGY OVERVIEW

SELECTED ABSTRACTS

ON

ARTIFICIAL SWEETENERS AND OTHER SUGAR SUBSTITUTES

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Selected Abstracts

On

ARTIFICIAL SWEETENERS AND OTHER SUGAR SUBSTITUTES

Ian C. Munro, Ph.D.
Consulting Reviewer

A Service of the International Cancer Research Data Bank (ICRDB) Program of the National Cancer Institute

HE20.3173/3:

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INTRODUCTION

This ONCOLOGY OVERVIEW on the chemical carcinogenesis of artificial sweeteners and other sugar substitutes includes abstracts selected from the CANCERLINE data base, referencing articles published mainly during 1975-1979. In some cases, selected information dating back to the 1960's is included for historical perspective. The strategy used for the on-line data base search is available on request from the CIDAC office and can be entered at any MEDLARS/MEDLINE terminal in order to obtain continuing updates in this area.

The scope of this agent oriented OVERVIEW deals with the carcinogenicity of artificial sweeteners and other sugar substitutes and their precursors and metabolites. Areas covered include studies of human exposure, epidemiology, animal carcinogenicity and modification of carcinogenicity. Also covered are metabolic, physiologic and morphologic effects of artificial sweeteners, genetic toxicity, and in vivo and in vitro testing. Chemical and physical properties of artificial sweeteners, and methods for their analysis, are also included. This OVERVIEW includes discussions of general health benefits of artificial sweeteners.

This ONCOLOGY OVERVIEW was prepared by Ian C. Munro, Ph.D., of the Toxicology Research Division of the Health Protection Branch of Health and Welfare, Canada, and Michael Feldman, M.S., of the CIDAC for Carcinogenesis Information, The Franklin Research Center.

EDITORIAL COMMENTARY

Epidemiological studies have not shown conclusively whether artificial sweeteners cause cancer in humans. One case-control study (1) suggested a positive association between bladder cancer incidence in males and consumption of saccharin, but other studies (2, 3) have been either negative or of insufficient sensitivity to detect small increases in risk. In some of these studies, total artificial sweetener intake was used as a measure of exposure, thus potential effects of saccharin and cyclamate cannot be assessed independently. There are no epidemiological data available on other sugar substitutes, such as xylitol or other polyols, that bear on the question of carcinogenesis.

There is no evidence that saccharin taken orally is metabolized by either man or other animals (4, 5). It is excreted almost completely in the urine. Cyclamates taken orally are metabolized the cyclohexylamine to varying degrees by intestinal microflora (6). Cyclohexylamine has been shown to produce testicular atrophy in rats. Xylitol and other polyols are metabolized via the pentose phosphate pathway and thus are converted to normal body metabolites.

With respect to carcinogenesis in animals, there is evidence that saccharin produces tumors of the urinary bladder in male rats, but only when exposure is commenced in utero (7, 8, 9). All other conventional studies have not shown saccharin or cyclamate to be carcinogenic. In some studies, saccharin and cyclamates enhanced the action of known carcinogens in the urinary bladder (10, 11), but in other studies (12) this was not the case. There is insufficient published information to assess the long term toxicity and potential carcinogenicity of xylitol or other polyols.

Saccharin and cyclamate have not been found to be mutagenic in most short-term tests for carcinogenicity (13), but saccharin promoted the action of 3-methylcholanthrene in an in vitro oncogenic transformation assay using fibroblasts (14). In some studies saccharin and cyclamate, as well as cyclohexylamine, have been shown to produce chromosomal damage (13, 15).

Chemical studies have shown that certain lots of sodium saccharin contain impurities that are mutagenic when tested by the Ames Salmonella assay (16). It is considered unlikely that these impurities contribute to the carcinogenicity of commercial saccharin, since they occur in minute concentrations and saccharin prepared by two different methods, each having qualitatively different impurities, have both been found to produce bladder tumors in male rats (7, 8, 9).

EDITOR'S NOTE: Some of the available information on the manufacture and uses of sweeteners are not published in the scientific literature. Also, many published studies relevant to the safety evaluation of sweeteners were not abstracted. References to this information listed by citation only may be found in appropriate chapters.

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16. Stoltz, D.R., Stavric, B., Klassen, R., Bendall, R.D., Craig, J. J. Environ. Pathol. Toxicol.; 1(1):139-146, 1977.

I. EPIDEMIOLOGICAL STUDIES, HUMAN EXPOSURE AND RELATED CLINICAL OBSERVATIONS

1. BLADDER CANCER MORTALITY IN DIABETICS IN RELATION TO SACCHARIN CONSUMPTION AND SMOKING HABITS.

Armstrong B, Doll R
Dept. Regius Professor of Medicine, Radcliffe Infirmary, Oxford OX2 6HE, England
Br J Prev Soc Med; 29:73-81 1975

The relationship between saccharin (SAC) use and bladder cancer in diabetics was assessed through analyses of data obtained from different sources. The frequency with which diabetes mellitus (DM) was mentioned on the death certificates of 18,733 patients who died of bladder cancer and 19,709 patients who died of other cancers (excluding cancer of the lung and pancreas) was determined. Comparisons of observed and expected numbers of deaths provided no evidence of an increased risk of bladder cancer in diabetics; the best estimate of this risk, relative to nondiabetics, was 0.98:1.0 with 95% confidence limits of 0.70-1.38. Information about the duration of DM was available for 88 patients who died of bladder cancer and 179 patients who died of other cancers. Estimates of risks were obtained from data on 23 patients who had DM and cancer diagnosed simultaneously; there was no increase in risk of bladder cancer in patients with DM of long duration, and the risk of death from bladder cancer in patients with DM of 20 or more yr duration was unlikely to be greater than 1.17:1.0. Based on a survey of 200 diabetics and 200 matched controls, it was found that diabetics consume a significantly higher amount of SAC-tablets, SAC-containing foods, and low-calorie soft drinks. Data on the smoking habits of diabetics were obtained from the Boston Collaborative Drug Surveillance Program; results indicate that the proportion of current smokers among diabetics was lower than among nondiabetics. There was no evidence that the consumption of above av amounts of SAC leads to bladder cancer in diabetics. (16 Refs)

2. BLADDER CANCER MORTALITY IN ENGLAND AND WALES IN RELATION TO CIGARETTE SMOKING AND SACCHARIN CONSUMPTION.

Armstrong B, Doll R
Radcliffe Infirm., Oxford, England
Br J Prev Soc Med; 28(4):233-240 1974

Cohort analyses of bladder cancer mortality in men and women in England and Wales were compared with figures for the per capita consumption of saccharin and cigarette tobacco and with similar analyses of cigarette smoking habits. That increases in bladder cancer mortality in men are due to cigarette smoking is supported by the correspondence between the first male cohorts to show a sharp increase in mortality (those born around 1865-1875) and the beginning of significant cigarette smoking by men (1890, when these cohorts had a mean age of 15-25 yr); and by the correspondence between the male cohort with peak bladder cancer mortality (that born around 1900) and that with the maximum percentage of cigarette smokers. In women, there are no clear increases in bladder cancer mortality corresponding to the mass increase in cigarette consumption starting in 1920. Trends in bladder cancer mortality in men and women show no evidence of any break in continuity that could be attributed to the use of saccharin since 1939. However, it may be too early to see an effect of saccharin consumption on mortality rates.

3. CANCER MORTALITY AND SACCHARIN CONSUMPTION IN DIABETICS.

Armstrong B, Lea AJ, Adelstein AM, Donovan JW, White GC, Ruttle S
Dept. Medicine, Univ. Western Australia, Australia
Br J Prev Soc Med; 30(3):151-157 1976

Saccharin consumption by members of the British Diabetic Association was studied to determine the relationship between saccharin consumption, diabetes, and cancer. Of 5,971 persons, 1,207 died; 778 deaths were expected from the mortality of the population of England and Wales. This excess of deaths was almost entirely due to diabetes mellitus and ischemic heart disease. Death from cancer (128) was less than expected (168), mainly because of a deficit in the number of deaths from cancer related to smoking. There was also a lower than expected mortality from chronic bronchitis and emphysema. More than half of the persons studied used saccharin tablets daily, with an overall daily intake of three to six tablets. About 23% of the patients would have taken saccharin daily for 10 yr or more and 10% for 25 yr or more by the end of the follow-up. It is concluded that these relatively high levels of saccharin intake did not increase the risk of cancer in the diabetics. (9 Refs)

4. CANCER MORTALITY AMONG DIABETICS.

Kessler II
Dept. Chronic Diseases, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 North Wolfe St., Baltimore, MD, 21205
JNCI; 44(3):673-686 1970

Cancer mortality was ascertained among 21,447 diabetic patients who registered at a large diabetes clinic in Boston during a 26-yr period ending in 1956. Observations were made through 1959. Analysis was by the calculation of standardized mortality ratios in which observed numbers of deaths were compared with numbers expected if the age- and sex-specific rates in the general Massachusettes population observed over the same period of time applied. Total cancer mortality among the female diabetics occurred at approx the expected frequency. By contrast, the male diabetics experienced a significantly reduced risk of cancer death that persisted even after the exclusion of deaths from lung cancer. This decreased cancer risk was believed attributable to two factors: a) an especially excessive risk of deaths from other causes, excluding cancer and b) an over-representation of Jews among the patients. The positive association between cancer and diabetes, reported in many clinical studies, is believed to be explained by the well-documented metabolic differences between normal and malignant tissues and by the failure of these studies to identify the antecedent disease. That diabetics have a significantly increased risk of death from pancreatic cancer was confirmed by this study. It is suggested that the carcinogenic potentialities of exogenous animal insulins be investigated, particularly in view of their known antigenic and teratogenic properties in laboratory animals. This study offers evidence that diabetic females do not have increased risk of

death from cancer of the uterine corpus. Earlier clinical reports of a high prevalence of diabetes among endometrial cancer patients almost invariably were based on retrospective observations which made it difficult to identify with certainty the antecedent disease. Mortality from lung cancer was reduced significantly among the male diabetics, but not among the females. An over-representation among the Jewish male patients (with their known diminished lung cancer risk) is believed responsible, at least in part. However, reduced lung cancer risk among diabetics independent of religion cannot be excluded. The possibility of differences in the cigarette smoking habits of diabetics and nondiabetics could not be examined. (Author abstract) (41 Refs)

5. NON-NUTRITIVE SWEETENERS AND HUMAN BLADDER CANCER: PRELIMINARY FINDINGS.

Kessler II

Dept. Epidemiology, The Johns Hopkins Univ. Sch. Hygiene and Public Health, Baltimore, MD

J Urol; 115(2):143-146 1976

The non-nutritive sweeteners, saccharin and cyclamate, were not associated with the risk of human bladder cancer in a controlled investigation. The prior intake of such sweeteners in any and all forms was not greater or more prolonged among 209 recently diagnosed bladder cancer patients than among 209 otherwise similar patients without bladder disease. These findings were unaffected by case-control differences in diabetic histories or smoking practices. (Author abstract) (20 Refs)

6. SACCHARIN, CYCLAMATE, AND HUMAN BLADDER CANCER. NO EVIDENCE OF AN ASSOCIATION.

Kessler II, Clark JP

Dept. Epidemiology and Preventive Medicine, Univ. Maryland Sch. Medicine, 655 W. Baltimore St., Baltimore, MD, 21201

JAMA; 240(4):349-355 1978

The results of a hospital-based case-control study of the possible roles of saccharine and cyclamate in human urinary bladder cancer are reported. The study groups consisted of 519 patients with histopathologically confirmed bladder cancer and 519 matched controls (cancer-free patients) from metropolitan Baltimore. All subjects were subjected to an intensive personal interview with respect to smoking habits, occupational history, and use of nonnutritive sweeteners (NNS). The proportions of patients and controls who ever used NNS in any form were the same (39.5%), and the frequency, quantity, or duration of intake of these substances did not differ significantly between the two groups. These normal findings persisted after simultaneous adjustment for the effects of smoking, occupation, age, diabetes mellitus, and several other potentially confounding factors. The failure of the relative risk of bladder cancer to increase with increasing NNS exposure is also inconsistent with an etiologic relationship. However, cyclamates were introduced too recently to permit the detection of carcinogenic effects appearing more than 10 or 15 yr after initial exposure. It is concluded that neither saccharin nor cyclamate is likely to be carcinogenic in man, at least at the moderate dietary levels reported by the patient sample. (18 Refs)

7. USE OF ARTIFICIAL SWEETENERS BY CANCER PATIENTS.

Morrison AS

Boston Collaborative Drug Surveillance Program, Boston Univ. Medical Center, 400 Totten Pond Road, Waltham, MA, 02154

J Natl Cancer Inst; 62(6):1397-1399 1979

Current daily use of artificial sweeteners (AS) and diet drinks was determined for 1,862 adult cancer patients from seven countries and for 10,874 control patients hospitalized for other conditions considered unrelated to the use of these substances. For all cancer sites combined, the age-standardized proportion of AS users was 2.8% for men and 6.0% for women; the percentages among controls were 6.1% for men and 9.5% for women. There were no AS users with cancer of the bladder, ureter, or renal pelvis and no male users with cancer of the stomach. However, 15.7% of the women with stomach cancer were AS users. Adjustment for country reduced but did not eliminate the case-control differences, and the inverse association between AS and cancer was not substantially changed by adjustment for smoking habits. The age sex country-standardized incidence of cancer among AS users was estimated at 1.0, based on interview of 455 cancer patients during their initial hospitalization for the disease. The age-standardized percentages of daily users of diet drinks were 0.6% and 0.8% among male cancer patients and controls, respectively, and 1.4% and 1.0% among female cancer patients and controls. The data do not support an overall positive association between AS and cancer. (22 Refs)

8. ARTIFICIAL SWEETENERS AND HUMAN BLADDER CANCER.

Howe GR, Burch JD, Miller AB, Morrison B, Gordon P, Weldon L, Chambers LW, Fodor G, Winsor GM

Epidemiology Unit, Natl. Cancer Inst. Canada, Univ. Toronto, Ontario, Canada

Lancet; 2(8038):578-581 1977

A study on the correlation between the use of artificial sweeteners and bladder cancer was conducted based on the results of questionnaires obtained from 480 men and 152 women with bladder cancer. The risk ratio for men who had used the sweeteners vs those who had never used them was 1.6; there was a significant dose-response relationship for both the duration and frequency of use. Joint controlling for both smoking and instant coffee consumption were used so that the relationship between these variables and artificial sweetener consumption was independent. It was not possible to determine the composition of each artificial sweetener used since the composition of saccharin and/or cyclamate had changed over the years; however, 82% of the men reported the use of saccharin only. Male diabetics who did not use sweeteners were at a decreased risk, but those who did use them had the same risk as the nondiabetic men. For women, there was a nonsignificant decreased use of artificial sweeteners among the cancer cases. (15 Refs)

9. SACCHARIN AND BLADDER CANCER (4 LETTERS TO EDITOR).

Miller AB, Howe GR, Burch JD, Kessler II, Clark JP, Gryder JW

Natl. Cancer Inst. Canada, Univ. Toronto, Toronto, Canada

JAMA; 241(10):996-998 1979

While Howe and coworkers (Lancet 2:578) reported a positive association between artificial sweeteners and human bladder cancer, Kessler and Clark reported that neither saccharin nor cyclamate was a likely human carcinogen. Methodological and biological inconsistencies are pointed out in these letters. Kessler and Clark agree with Ryder that pregnant or lactating women should avoid or reduce saccharin intake. (12 Refs)

10. ARTIFICIAL SWEETENERS AND BLADDER CANCER (LETTER TO EDITOR).

Miller AB, Howe GR

Epidemiology Unit, Natl. Cancer Inst. Canada, Univ. Toronto, Toronto, Ontario, Canada

Lancet; 2(8050):1221-1222 1977

The Canadian study that found a positive association between artificial sweeteners consumption and male bladder

cancer is reviewed. Topics include selection of controls according to matched and unmatched variables and differences in sweetener use for men and women. If the observed association between artificial sweeteners and male bladder cancer is not due to chance, then it must be (1) real, (2) due to confounding, or (3) due to bias or error in study design and execution. The study of the last two being true is discussed. (11 Refs)

11. SYNTHETIC SWEETENER CONSUMPTION AND BLADDER CANCER TRENDS IN THE UNITED STATES.

Burbank F, Fraumeni JF
NCI, Bethesda, Md.
Nature (Lond); 227(5255):296-297 1970

In a study of the general use of cyclamates and the toxicity of artificial sweeteners, the U.S. Department of Health, Education and Welfare found no clear-cut separation in age-specific or age-adjusted mortality rates for bladder cancer from 1950-1967, inclusive (1962 being the yr cyclamate consumption dramatically increased). Incidence rates for bladder cancer showed only a long-term increase in rate (by about 8/100,000 over the 17-yr period) which may be related to cigarette smoking. As yet, bladder cancer rates do not appear affected by synthetic sweeteners, but the time period is considered too short and the dosage too low for examples of cyclamate carcinogenicity to have appeared. Chromosome breaks in vivo in rats and in vitro in human cells due to cyclamates and cyclohexylamine are also mentioned.

12. SACCHARIN AND BLADDER CANCER.

Schmahl D
Institut fur Toxikologie und Chemotherapie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld, 6900 Heidelberg, W. Germany
Dtsch Med Wochenschr; 103(3):91-92 1978

The data indicating that saccharin causes bladder cancer in humans are briefly reviewed. Epidemiological studies done in England and the United States did not indicate that the incidence of bladder cancer was higher in saccharin users than in nonusers. (7 Refs)

13. SEX-SPECIFIC CARCINOGENS, WITH SPECIAL REFERENCE TO SACCHARIN. (LETTER TO EDITOR).

Wigle DT
Cancer Section, Bureau Epidemiology, Lab. Centre for Disease Control, Health and Welfare Canada, Ottawa, Ontario K1A 0L2, Canada
Lancet; 1(8058):279 1978

Criticism of the sex specificity of saccharin carcinogenesis in man, based on the argument that no nonhormonal carcinogen in man is sex specific, is stated to be invalid. Animal studies have revealed at least 22 sex-specific carcinogens that cause tumors such as hepatomas, lymphomas, sarcomas, and mixed tumors.

14. THREE CASES OF HUMAN BLADDER CANCER FOLLOWING HIGH DOSE CYCLAMATE INGESTION.

Barkin M, Comisarow RH, Taranger LA, Canada A
Div. Urology, Sunnybrook Medical Center, 2075 Bayview Ave., Toronto, Canada
J Urol; 118(2):258-259 1977

Three men, aged 66, 49, and 64 yr, each developed transitional cell carcinoma of the bladder after ingestion of large quantities of cyclamate over a long period of time. It is suggested that bladder cancer patients be questioned about their intake of cyclamates. (17 Refs)

15. BLADDER CANCER: SMOKING, BEVERAGES AND ARTIFICIAL SWEETENERS.

Morgan RW, Jain MG
Dept. Preventive Medicine, Sch. Hygiene, Univ. Toronto, Toronto, Ontario M5S 1A1, Canada
Can Med Assoc J; 3:1067-1070 1974

A matched patient-control study of bladder cancer examined the relationship of the disease to occupation, smoking and intake of tea, coffee, cola, alcohol and artificial sweeteners. There was no association of disease with occupation for these patients. Heavy smoking gave relative risks of 6.37 and 4.36 for men and women respectively; there was evidence of a dose-response relationship. Tea and coffee intake did not increase the risk of disease nor did prolonged use of artificial sweeteners. Alcohol and cola intake increased the relative risk of bladder cancer among male smokers. There is some suggestion that smoking interacts with both alcohol and cola intake in the production of bladder cancer. (Author abstract) (22 Refs)

16. SACCHARIN PLUS CIGARETTES TIED TO BLADDER CANCER IN MEN.

Anonymous
No affiliation given
Med World; 20(11):10-11 1979

The possibility that not saccharin (SC) alone but SC plus cigarette smoking increases the risk of bladder cancer (BlC) in men has emerged from a dispute over new and old interpretations of old epidemiological data. The author of a study of 260 men and 86 women with BlC and 2,235 men and 1,602 women without BlC had initially concluded that there was no association between SC use and BlC. However, the author's second look at his data showed that the cancer risk was almost triple for men who consumed SC and were also moderate cigarette smokers. This reversal, which was sent to the National Cancer Institute in November 1977, took 18 mo to surface. (no Refs)

17. COFFEE DRINKING AND CANCER OF THE LOWER URINARY TRACT.

Simon D, Yen S, Cole P
Harvard Sch. Public Health, Boston, Mass.
J Natl Cancer Inst; 54(3):587-591 1975

Coffee drinking habits of urban white women from Massachusetts and Rhode Island were studied for a possible relationship to lower urinary tract (LUT) cancer. Patients with LUT cancer were chosen from the pathology log book and diagnostic index of participating hospitals. Three white women were chosen as controls for each case. Data on coffee drinking and related habits were obtained by mail questionnare for 135 women with LUT cancer and for 390 controls; questions included age when coffee drinking and cigarette smoking began, usual daily consumption of coffee, cigarettes, and tea, occupation, coffee additives used, and type and strength of coffee. The risk ratio for women who drank one or more cups of coffee per day was 2.1 when compared to women who drank no coffee or less than one cup per day. However, the amount of coffee consumed showed no relationship to dose-response. The type of coffee, the strength of the coffee or the use of creamers or sugar substitutes (i.e saccharin or cyclamates) was not associated with increased risk of disease. The risk of LUT cancer for cigarette smokers as compared to nonsmokers was 1.6. The results suggest that the association of coffee drinking with LUT cancer is noncausal.

18. THE EPIDEMIOLOGY OF BLADDER CANCER. A SECOND LOOK.
Wynder EL, Goldsmith R
American Health Foundation, 1370 Ave. of the Americas, New York, NY 10019
Cancer; 40(3):1246-1268 1977

The epidemiology of bladder cancer is considered based on a case-control study of 574 men and 158 women seen over a 5-yr period, and these results are compared to those from previous investigations. Bladder cancer occurs more in men than in women, except in Egypt, where both sexes are exposed to Schistosoma hematobium and the incidence is about equal. Bladder cancer also affects nearly twice as many white men and women as black women. Cigarette smokers of both sexes were at a higher risk than non-smokers. About 50% of the male cases and 33% of the female cases were attributed to cigarette smoking; there was a fairly consistent dose-response relationship for amount and duration of smoking in both sexes. However, no significant differences were observed between the proportions of cases and controls who used pipes, cigars, chewing tobacco or snuff. There was also an excess of bladder cancer in persons with occupational exposure to rubber, chemicals and textiles. An increase in risk with coffee drinking was noted in both sexes; this increase was slightly higher in men and was independent of smoking levels. No relationship was found between alcohol consumption and bladder cancer. No association was found for artificial sweeteners. It is suggested that further studies concentrate on metabolic factors since cigarette smoking and occupational exposure did account fully for the observed incidence. (120 Refs)

19. A NEW PHOTOSENSITIZER. THE ARTIFICIAL SWEETENER CYCLAMATE.
Lamberg SI
J Am Med Assoc; 201:747-750 1967

20. SPONTANEOUS ABORTION AND THE USE OF SUGAR SUBSTITUTES (SACCHARIN).
Kline J, Stein ZA, Susser M, Warburton D
Am J Obstet Gynecol; 130:708-711 1978

21. DO ARTIFICIAL SWEETENERS INGESTED IN PREGNANCY AFFECT THE OFFSPRING?
Stone D, Matalka E, Pulaski B
Nature (Lond); 231:53 1971

22. UNTOWARD REACTION OF SACCHARIN.
Taub SJ
Eye Ear Nose Throat Mon; 51:405 1972

23. CYCLOHEXYLAMINE, P-CHLORNITROBENZENE, 2-AMINOPYRIDINE: TOXIC EFFECTS IN INDUSTRIAL USE.
Watrous RM, Schulz HN
Ind Med Surg; 19:317-320 1950

24. PHOTOSENSITIVE DERMATITIS AND RENAL TUBULAR ACIDODID AFTER INGESTION OF CALCIUM CYCLAMATE.
Yong JM, Sanderson KV
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II. PHARMACOKINETICS AND METABOLISM

A. Pharmacokinetics and Metabolism of Artificial Sweeteners in Human Subjects

29. FURTHER OBSERVATIONS ON THE METABOLISM OF SACCHARIN IN MAN (MEETING ABSTRACT).
Byard JL, Goldberg EW, Coulston F
Inst. Comparative Human Toxicology, Albany, NY
Toxicol Appl Pharmacol; 29(1):154-155 1974

Each of four men took 500 mg of ^{14}C saccharin (9.8 microCi), and their excreta were collected at intervals up to 96 hr. Over 98% of the ^{14}C was recovered within 48 hr (92.1% in urine, 5.8% in feces), and only a further amount of 0.3% was excreted over 48-72 hr (none over 72-96 hr). The mean 24 hr excretion of 92.4% of the dose indicates a body half-life of about 6.5 hr. In most of the urine samples, gas-liquid chromatographic (GLC) analysis gave results for saccharin (SA) corresponding very closely to those calculated from the ^{14}C counts, but in several there were discrepancies exceeding considerably those expected from the precision (+-3%) of the GLC method. Very high values in two samples made it likely that the subject had inadvertently ingested extraneous SA, while two low values (both in 0-8 hr samples) suggested that some alteration of the administered SA had occurred. However, chromatographic analysis failed to reveal the presence in these samples of labeled compounds other than SA in more than trace amounts. Hydrolysis of the aberrantly low samples with strong alkali brought the GLC and ^{14}C analyses into satisfactory agreement. The fecal ^{14}C proved to be in the form of unchanged SA. Subsequently, these same subjects, together with two others, took 500 mg of unlabeled SA; urine only was collected for the ensuing 72 hr. Analysis of these samples by GLC gave rates of excretion quite similar to those described above: the mean overall 72 hr excretion as SA was 90.3% of the dose, but alkaline hydrolysis brought this figure up to 94.3%. These results substantiate earlier findings in animals.

30. THE FATE OF CYCLAMATE IN MAN AND OTHER SPECIES.

Renwick AG, Williams RT
Department of Biochemistry, St. Mary's Hospital Medical School, London W.2, U.K.
Biochem J; 129:869-879 1972

14C-labelled cyclamate has been administered to guinea pigs, rabbits, rats and humans. When given orally to these species on a cyclamate-free diet, cyclamate in excreted unchanged. In guinea pigs some 65% of a single dose is excreted in the urine and 30% in the faeces, the corresponding values for rats being 40 and 50%, for man, 30-50% and 40-60%, and for rabbits, 90 and 5%, the excretion being over a period of 2-3 days. Cyclamate appears to be readily absorbed by rabbits but less readily by guinea pigs, rats and humans. If these animals, including man, are placed on a diet containing cyclamate they develop the ability to convert orally administered cyclamate into cyclohexylamine and consequently into the metabolites of the latter. The extent to which this ability develops is variable, the development occurring more readily in rats than in rabbits or guinea pigs. In three human subjects, one developed the ability quite markedly in 10 days whereas two others did not in 30 days. Removal of the cyclamate from the diet caused a diminution in the ability to convert cyclamate into the amine. In rats that had developed the ability to metabolize orally administered cyclamate, intraperitoneally injected cyclamate was not metabolized and excreted unchanged in the urine. The biliary excretion of injected cyclamate in rats was very small, i.e. about 0.3% of the dose. The ability of animals to convert cyclamate into cyclohexylamine appears to depend upon a continuous intake of cyclamate and on some factor in the gastrointestinal tract, probably the gut flora.

31. EXCRETION OF CYCLOHEXYLAMINE, A METABOLITE OF CYCLAMATE, IN HUMAN URINE.

Asahina M, Yamaha T, Watanabe K, Sarrazin G
Natl. Inst. Hyg. Sci., Tokyo, Japan
Chem Pharm Bull (Tokyo); 19(3):628-632 1971

Five normal and 1 diabetic volunteer were given 2 g of sodium cyclamate (CHS-Na) in a single dose, after which 24 hr urine specimens were assayed over 5 days for the presence of CHS-Na and cyclohexylamine (CHA). In 3 cases, most of the CHS-Na (e.g. about 1.5 g) was excreted on the first day; 2 persons excreted maximum amounts of CHS-Na on day 2. Two of the subjects did not excrete appreciable amounts of CHA, while the other 3 excreted between 0.4-0,8 g of CHA from day 2 to day 5. Approximately 33-81% of the ingested CHS-Na as such and 1-18% as CHA were recovered form the urine of subjects. In a related experiment, urinary excretion of CHS-Na and CHA was monitored in 50 volunteers (49 men, 1 woman) eating normal meals during a 2 month period; cyclamate was found in the urine of all volunteers in amounts ranging from 1-700 mg/day. Forty-three of the volunteers excreted CHA, 9 of them more than 10 mg.

32. THE METABOLITES OF CYCLOHEXYLAMINE IN MAN AND CERTAIN ANIMALS.

Renwick AG, Williams RT
Department of Biochemistry, St. Mary's Hospital Medical School, London W.2, U.K.
Biochem J; 129:857-867 1972

1-14CCyclohexylamine hydrochloride was synthesized and given orally or intrperitoneally to rats, rabbits and guinea pigs (dose 50-500 mg/kg) and orally to humans (dose 25 or 200 mg/person). The 14C is excreted mainly in the urine, most of the excretion occurring in the first day after dosing. Only small amounts (1-7%) are found in the faeces. In the rat, guinea pig and man, the amine is largely excreted unchanged, only 4-5% of the dose being metabolized in 24h in the rat and guinea pig and 1-2% in man. In the rabbit about two-thirds of the dose is excreted unchanged and about 30% is metabolized. In the rat, five minor metabolites were found, namely cyclohexanol (0.05%), trans-3- (2.2%), cis-4- (1.7%), trans-4- (0.5%) and cis-3-aminocyclohexanol(0.1% of the dose in 24h). In the rabbit, eight metabolites were identified, namely cyclohexanol (9.3%), trans-cyclohexane-1,2-diol (4.7%), cyclohexanone (0.2%), cyclohexlhydroxylamine (0.2%) and trans-3- (11.3%), cis-3- (0.6%), trans-4- (0.4%) and cis-4-aminocyclohexanol (0.2%). In the guinea pig, six minor metabolites were found, namely cyclohexanol (0.5%), trans-cyclohexane-1,2-diol (2.5%) and trans-3- (1.2%), cis-3- (0.2%), trans-4- (0.2%) and cis-4-aminocyclohexanol (0.2%). In man only two metabolites were definitely identified, namely cyclohexanol (0.2%) and trans-cyclohexane-1,2-diol (1.4% of the dose), but man had been given a smaller dose (3 mg/kg) than the other species (50 mg/kg). The hydroxylated metabolites of cyclohexylamine were excreted in the urine in both free and conjugated forms. Although cyclohexylamine is metabolized to only a minor extent, in rats the metabolism was mainly through hydroxylation of the cyclohexane ring, in man by deamination and in guinea pigs and rabbits by ring hydroxylation and deamination.

33. XYLITOL ABSORPTION IN HEALTHY MEN.

Asano T, Levitt MD, Goetz FC
Diabetes; 22:279-281 1973

34. XYLITOL ABSORPTION IN HEALTHY MEN.

Asano T, Levitt MD, Goetz FC
Diabetes Suppl; 21:350-351 1972

35. EXCRETION OF CYCLOHEXYLAMINE IN SUBJECTS INGESTING SODIUM CYCLAMATE.

Davis TR, Adler N, Opsahl JC
Toxicol Appl Pharmacol; 15:106-116 1969

36. PHARMACOKINETICS, CARDIOVASCULAR AND METABOLIC ACTIONS OF CYCLOHEXYLAMINE IN MAN.

Eichelbaum M, Hengstmann JH, Rost HD, Brecht T, Dengler HJ
Arch Toxicol; 31:243-263 1974

37. CYCLAMATE DEGRADATION IN MAMMALS AND IN VITRO.

Golberg L, Parekh C, Patti A, Soike K
Toxicol Appl Pharmacol; 14:654 1969

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Chem Pharm Bull; 17:2620-2625 1969

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Leahy JS, Wakefield M, Taylor T
Food Cosmet Toxicol; 5:447 1967

40. CYCLOHEXYLAMINE PRODUCTION AND PHYSIOLOGICAL MEASUREMENTS IN SUBJECTS INGESTING SODIUM CYCLAMATE.

Litchfield MH, Swan AA
Toxicol Appl Pharmacol; 18:535-541 1971

41. EXCRETION AND METABOLISM OF SACCHARIN IN MAN. I. METHODS OF INVESTIGATION AND PRELIMINARY RESULTS.
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42. DIETARY CYCLAMATE AND CYCLOHEXYLAMINE EXCRETION IN MAN.
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Proc Nutr Soc; 29:10A-11A 1970

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Am J Obstet Gynecol; 108:1042-1050 1970

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Sonders RC, Wiegand RG
Toxicol Appl Pharmacol; 12:291 1968

45. XYLITOL METABOLISM IN HEALTHY, LIVER-DISEASED AND DIABETIC PEOPLE. (TRANSLATED TITLE)
Mehnert H, Summa JD, Forster H
Klin Wochenschr; 42:382 1964

46. THE METABOLISM OF CERTAIN DRUGS AND FOOD CHEMICAL IN MAN.
Williams RT
Ann NY Acad Sci; 179:141-154 1971

47. A THREE-MONTH STUDY OF DAILY INTAKE OF SODIUM CYCLAMATE BY MAN.
Wills JH, Jameson E, Stoewsand G, Coulston F
Toxicol Appl Pharmacol; 12:292 1968

48. CLINICAL APPLICATION OF XYLITOL IN DIABETICS.
Yamagata S, Goto Y, Ohneda A, Anzai M, Kwashima S, Kikuchi J, Chiba M, Maruhama Y, Yamauchi Y, Toyota T
International Synposium on Metabolism, Physiology and Clinical Use of Pentoses and Pentitols, Hakone. Horecker BL, ed. pp. 316-325, 1967.

49. INFLUENCE OF SACCHARIN ON THE NUTRITION AND HEALTH OF MAN.
U.S. Department of Agriculture
Influence of Saccharin on the Nutrition and Health of Man. U.S. Department of Agriculture, Washington, D.C., Report # 94, 1911.

B. Pharmacokinetics and Metabolism of Artificial Sweeteners in Laboratory Animals

50. ABSORPTION OF SACCHARIN FROM RAT URINARY BLADDER (LETTER TO EDITOR).
Colburn WA
Dept. Biochemistry and Drug Metabolism, Hoffmann-La Roche, Inc., Nutley, NY, 07110
J Pharm Sci; 67(10):1493-1494 1978

Measurements of plasma levels of saccharin following in vivo instillation of 10 ug or 1 or 100 mg/kg of the compound into the urinary bladder of male Sprague-Dawley rats showed that this substance was absorbed extensively from the bladder. Significant reabsorption may decrease the elimination rate for saccharin in much the same way as enterohepatic cycling and probably accounts for the retention of saccharin in urinary bladder tissue. (3 Refs)

51. SACCHARIN METABOLISM AND TUMORIGENICITY.
Sweatman TW, Renwick AG
Clinical Pharmacology Group, Univ. Southamptom, Medical and Biological Sciences Bldg., Southampton S09 3TU, England
Science; 205(4410):1019-1020 1979

Adult male Charles River CD1 rats that had been exposed to saccharin in utero and maintained on a 5% saccharin diet were given free access to a diet containing 5% 3Hsaccharin for 24 hr and then returned to the unlabeled diet (pulsed-dose experiment). In another experiment, normal rats received a single dose of 3Hsaccharin (60 ug/kg) by intubation or 3-methylcholanthrene (MCA: 20 mg/kg, po) 3 and 2 days before a single dose of 3Hsaccharin (400 mu/kg, po). The 3H label was eliminated, largely in the urine, within 48 hr. In the pulsed-dose experiment, fecal excretion was 14%, while in the two other experiments, fecal excretion was 2.5%-3% in rats given the 60 ug/kg dose and 6.5%-8% in rats treated with MCA and 400 ug/kg saccharin. Urine samples obtained 0-24 hr after labeled saccharin administration in the pulsed-dose experiment contained 98.5% saccharin and less than 0.05% 2-sulfamoylbenzoic acid. Similar results were obtained in the untreated rats given 60 ug/kg saccharin. These results demonstrate that significant metabolism is not induced by long-term saccharin administration during the neonatal and weaning stages of two-generation studies. The possibility that the carcinogenic effects of saccharin are due to the unmetabolized parent compound, to a promoting effect, or to changes in physiological function should be investigated. (11 Refs)

52. THE FATE OF ^{14}CSACCHARIN IN MAN, RAT AND RABBIT AND OF 2-SULPHAMOYL^{14}CBENZOIC ACID IN THE RAT.
Ball LM, Renwick AG, Williams RT
Dept. Biochemistry, St. Mary's Hosp. Medical Sch., London W2 1PG, England
Xenobiotica; 7(4):189-203 1977

The effect of prolonged exposure to dietary saccharin on the metabolism and excretion of ^{14}C-saccharin was studied in rats, rabbits, and humans. ^{14}C-Saccharin administered po was excreted entirely unchanged by rats and rabbits on a normal diet, by rats on a 1% and 5% saccharin diet for up to 12 mo, and by rabbits on a 1% saccharin diet for 6 mo. In the rat 90% of the dose was excreted in 24 hr, 70%-80% in the urine and 10%-20% in the feces. In the rabbit, 60%-80% of the dose was excreted in 24 hr, with 70% in urine and 3%-11% in feces. 3-^{14}C-Saccharin taken po by three adult humans (1 woman, 2 men) was also excreted unchanged, 85%-92% in the urine in 24 hr both before and after taking 1 g of saccharin daily for 21 days. Saccharin was not metabolized in vitro by liver microsomal preparations nor by fecal homogenates from normal or saccharin-fed rats or by fecal homogenates from rats capable of converting cyclamate to cyclohexylamine. 2-Sulfamoyl-^{14}C-benzoic acid given po to rats was excreted unchanged more slowly than saccharin. Saccharin clears less rapidly from the urinary bladder of both adult and fetal rats than from other tissues, suggesting that the bladder may be a target for any toxic action of saccharin. Whether this applies to man is not known. (30 Refs)

53. THE FATE OF SACCHARIN IMPURITIES: THE EXCRETION AND METABOLISM OF TOLUENE-2-SULPHONAMIDE IN MAN AND RAT.

Renwick AG, Ball LM, Corina DL, Williams RT
Pharmacology, Faculty Medicine, Univ. Southampton, Southampton SO9 3TU, England

Xenobiotica; 8(8):461-474 1978

Oral doses (20 mg/kg) of Me-14Ctoluene-2-sulphonamide were rapidly eliminated by rats (92% of dose in 24 hr). Most of the 14C (88%) was recovered in the urine within 7 days with little (5%) in the feces. Larger oral doses (125 and 200 mg/kg) were eliminated more slowly (70 and 43% respectively in 24 hr) but the overall distribution of 14C between urine and feces was unchanged. Low oral dose (0.2-0.4 mg/kg) of Me-14Ctoluene-2-sulphonamide were excreted more slowly in man than in the rat, with about 50% recovered in the urine in 24 hr and 80% in 48 hr. Negligible 14C (less than 1%) appeared in the feces. The main metabolites of toluene-2-sulphonamide were 2-sulphamoylbenzyl alcohol and its sulphate and glucuronic acid conjugates (80% of the 14C in the urine of rats and 35% in man) and saccharin (35% in man and 3% in the rat). Other metabolites found in the urine were 2-sulphamoylbenzoic acid (2% in the rat and 4% in man) and N-acetyltoluene-2-sulphonamide (6% in rat and 2% in man) together with unchanged compound (5% in rat and 3% in man). (Author abstract) (13 Refs)

54. THE FATE OF SACCHARIN IMPURITIES: THE EXCRETION AND METABOLISM OF 3-"CBENZDISOTHIAZOLINE-1,1-DIOXIDE (BIT) IN MAN AND RAT.

Renwick AG, Williams RT
Pharmacology, Faculty Medicine, Univ. Southampton, Southampton SO9 3TU, England

Xenobiotica; 8(8):475-486 1978

The 14C label of 3-14Cbenzdisothiazoline-1,1-dioxide (BIT) (40 mg/kg) was rapidly eliminated (97% dose in 24 hr), largely in the urine (92% dose in 24 hr), after oral administration to rats. Larger doses (400 mg/kg) were eliminated more slowly after oral or parenteral administration (45-60% within 24 hr) mostly in the urine (42-53%). Little 14C (2-3% dose) was present in the feces after ip (400 mg/kg) or low oral (40 mg/kg) doses, but the presence of larger amounts (12% dose) after larger oral doses (400 mg/kg) indicated incomplete absorption. Metabolites identified in the urine of rats were saccharin (about 30% of urinary 14C), 2-sulphamoylbenzoic acid (about 35% urinary 14C) and 2-sulphamoylbenzyl alcohol (15% urinary 14C) in addition to unchanged compound (5-10% urinary 14C). The urine also contained a polar, labile metabolite that gave BIT on acid hydrolysis. The pattern of metabolism was not significantly affected by dose or route of administration. In man, urine was the major route of elimination of 14C (93% dose) after administration of 14C-BIT (0.5 mg/kg). Negligible 14C was recovered in the feces (less than 1% dose). Excretion was rapid (59% dose in 6 hr; 80% dose in 12 hr) and little 14C was eliminated on the second (3%) or subsequent days after dosing. Identified metabolites in man included saccharin (about 50% of urinary 14C), 2-sulphamoylbenzoic acid (7% urinary 14C) and 2-sulphamoylbenzyl alcohol (8% urinary 14C unconjugated and 40% conjugated) with negligible unchanged compound. Only traces of the polar labile metabolite were detected. The possible significance of metabolic interrelationships of toluene-2-sulphonamide and BIT to studies on the metabolism of saccharin are discussed. (Author abstract) (12 Refs)

55. THE FATE OF SACCHARIN IMPURITIES. THE EXCRETION AND METABOLISM OF "CTOLUENE-4-SULPHONAMIDE AND 4-SULPHAMOYL"CBENZOIC ACID IN THE RAT.

Ball LM, Williams RT, Renwick AG
Pharmacology Branch, NIEHS, Research Triangle Park, NC, 27709

Xenobiotica; 8(3):183-190 1978

The fate of "C-labeled toluene-4-sulfonamide (TS) and 4-sulfamoylbenzoic acid (SBA), byproducts of saccharin synthesis by the Remsen-Fahlberg process, was determined in female albino Wistar rats. The rats were given 29 or 200 mg/kg TS or 22 mg/kg SBA by intragastric intubation. Approx 94% of the SBA dose was eliminated within 24 hr. By 6 days, 73%-83% of the dose was recovered in the urine, but significant amounts (18%-32%) were eliminated in the feces because of incomplete absorption. The "C in the urine and feces was unchanged SBA. No labeled CO2 was detected in the expired air. Following TS administration, 66%-89% of the dose was rapidly eliminated in the urine, with only 2%-8% being eliminated in the feces. The label in the feces was SBA; it probably originated in the tissues, since the gut flora could not effect this biotransformation. The urine of rats given TS contained SBA as the major metabolite (93% of the urinary label), together with small amounts of unchanged TS (1.5%-2.3% of the label), 4-sulfamoylbenzyl alcohol (2.0%-3.9%) 4-sulfamoylbenzaldehyde (0%-1.5%: at the lower dose only), and N-acetyltoluene-4-sulfonamide (2.1%-2.3%: at the higher dose only). Thus, prolonged intake of saccharin containing traces of TS and SBA should not lead to their accumulation in the body, providing that the larger amounts of saccharin do not interfere with the oxidation of TS to SBA or the renal elimination of the latter. (14 Refs)

56. THE FATE OF SACCHARIN IMPURITIES: THE METABOLISM AND EXCRETION OF 3-AMINO3-"CBENZDISOTHIAZOLE-1,1-DIOXIDE AND 5-CHLOROSACCHARIN IN THE RAT.

Renwick AG
Univ. Southampton, Bassett Cresent East, Southampton SO9 3TU, England

Xenobiotica; 8(8):487-494 1978

The metabolism of 3-amino3-14Cbenzodisothiazole-1,1-dioxide, prepared from 3-14C-saccharin was studied. It was well absorbed on oral administration to rats (25 mg/kg) with only 2% of the 14C in the feces. The absorbed material was rapidly eliminated with about 87% dose in the urine in 24 hr and 91% in 4 days. Little 14C (0.5 of dose) was present in the carcass 4 days after dosing. Most of the 14C in the 0-24 hr urine (99%) was present as unchanged 3-aminobenzdisothiazole-1,1-dioxide, the rest being an unidentified metabolite. 5-Chlorosaccharin was excreted, unchanged after oral administration to rats (80 mg/kg) with 76% dose in the urine in 24 hr and 81% in 4 days. Only 4% was detected in the feces. There was no significant hydrolysis (less than 0.5%) to 5-chloro-2-sulphamoylbenzoic acid. The extent of metabolism of these and other compounds related to saccharin showed good agreement with the extent of their partitioning into organic solvents. (Author abstract) (6 Refs)

57. DISCONTINUITIES IN DOSE RESPONSE CURVES FROM TOXICOLOGICAL TESTS.

Anderson RL
Procter and Gamble Co., Miami Valley Labs., Cincinnati, OH

Household Pers Prod Ind; 16(4):92,94 1979

Nonlinear dose-related shifts in urinary pH and increases in urinary calcium, magnesium, and phosphorus excretion occurred in rats fed sodium saccharin in doses of up to 7.5%.

These and further observations suggested that saccharin influences the normal metabolic pathways for nitrogen excretion and disturbs the acid/base balance. It is possible that shifts in the cellular environment produce changes in urinary tract cells via physical forces and not via chemically induced changes in cellular constituents. (1 Ref)

58. THE EXPOSURE OF FETAL AND SUCKLING RATS TO SACCHARIN FROM DOSED MATERNAL ANIMALS.

West RW
Natl. Center Toxicological Res., Div. Carcinogenesis, Jefferson, AR, 72079
Toxicol Lett; 4(3):127-133 1979

The distribution of radiolabeled saccharin was studied in pregnant and lactating Sprague-Dawley rats given 5% dietary saccharin. Saccharin crossed the placenta and entered the fetal circulation and was excreted in the milk. The ratio of the fetal blood level of saccharin to the maternal blood level after parturition increased with time after saccharin administration. (14 Refs)

59. WHOLE-BODY AUTORADIOGRAPHY OF 14C SODIUM CYCLAMATE IN PREGNANT AND FETAL RATS.

Schechter PJ, Roth LJ
Dept. Pharmacol., U. Chicago, Ill.
Toxicol Appl Pharmacol; 21(1):130-133 1971

The relative distribution of 14C sodium cyclamate in fetal and maternal tissues of the full-term pregnant rat was investigated immediately after injection and at a time point corresponding to the estimated biological half-life of the compound. Adult non-pregnant and 21-day pregnant Sprague-Dawley rats were injected iv with 100 mg/kg of uniformly labeled 14C-sodium cyclamate. The animals were sacrificed at five min and at seven hr after injection. Whole body autoradiograms from saggital sections of each animal were prepared. It was found that five min after injection into 21-day pregnant rats the isotope was seen to be distributed relatively evenly throughout the maternal tissues. A similar distribution was observed in nonpregnant females at five min after injection. The fetuses contained little or no radioactivity at this time. At seven hr after iv injection, most of the radioactivity had disappeared from maternal organs. The same distribution was seen in the nonpregnant female at this time point. In contrast to the mother, the fetuses retained a significant amount or radioactivity in all organs visible. It was suggested that a more intensive study of possible adverse effects of cyclamate on the embryo and fetus (with special emphasis on the urinary bladder) are needed.

60. THE METABOLISM OF CYCLAMATES IN RATS.

Wallace WC, Lethco EJ, Brouwer EA
Food Drug Admin., Dept. Hlth. Educ. Welfare, Washington, D.C.
Pharmacol Exp Ther; 175(2):325-330 1970

Weanling rats of both sexes were fed cyclamates in their diet (0.4, 2.0, or 10%) for a year or more, after which 63 of them were given a po intubation of 14C- cyclamate (2 microC or 2.2 mg). Essentially all of the administered dose was accounted for in the excreta after 3 days, with 35% appearing in the urine. The cyclamate was converted to cyclohexylamine in 83% of the rats; amounts ranged from less than 0.1-38%. Small quantities of cyclohexylamine were also found in the feces. No metabolite other than cyclohexylamine was detectable. Although no attempt was made to determine at what stage during the feeding period the conversion of cyclamate to cyclohexylamine took place, prolonged or chronic feeding seemed to potentiate this conversion process. No significant amounts of excreted cyclamates were found in the bile.

61. DISTRIBUTION OF 14C-CYCLAMATE IN THE LACTATING RAT.

Ward VL, Zeman FJ
Department of Nutrition, University of California, Davis, California 95616
J Nutr; 101:1635-1646 1971

Mammary excretion of cyclamate was studied in lactating rats. 14C-cyclamate was given to the rats by intravenous injection, and its movement was followed by scintillation counting and autoradiography. Simulation analysis was used in the interpretation of experimental results. Cyclamate was found to travel rapidly throughout the body, quickly reaching an initial equilibrium between the unionized fractions found in blood and milk. Kidney excretion let to an exponential decline of cyclamate from all samples other than milk, causing the concentration of cyclamate in milk to exceed that in the blood within approximately 1 hour. The very slow decline of cyclamate from the milk was shown to be primarily the result of the normal process of milk synthesis.

62. THE ROLE OF THE GUT FLORA IN THE METABOLISM OF CYCLAMATE.

Drasar BS, Renwick AG, Williams RT
Department of Bacteriology and Biochemistry, St. Mary's Hospital Medical School, London W.2, U.K.
Biochem J; 129:881-890 1972

14CCyclamate was not metabolized when incubated with the liver, spleen, kidney or blood of rats or rabbits kept on a cyclamate-containing diet, and that had become converters of cyclamate into cyclohexylamine. 14CCyclamate was converted into cyclohexylamine when incubated under anaerobic conditions with the contents of the caecum, colon or rectum or with the faeces of cyclamate-pretreated rats. Similar results were obtained with cyclamate-pretreated rabbits. With cyclamate-pretreated guinea pigs, which did not readily convert cyclamate into cyclohexylamine, the colon contents showed only low activity in this respect. The faeces of a human converter of 14Ccyclamate into cyclohexylamine were also very active, but became less active when cyclamate was removed from his diet. On subculturing the organisms from the contents of the colon and rectum of rats, the ability to convert cyclamate into cyclohexylamine was lost during three subcultures, but the loss of the activity was considerably decreased by subculturing in the presence of cyclamate. Incubation of rat faeces in broths containing cyclamate increased their ability to metabolize cyclamate, but similar treatment of rabbit and human faeces suppressed this activity. When rats are kept on a cyclamate diet the number of clostridia in the faeces increased considerably. In humans dietary cyclamate did not appear to alter the counts of various faecal micro-organisms. The gut organisms that appear to develop the ability to convert cyclamate into cyclohexylamine are clostridia in rats, enterobacteria in rabbits and enterococci in man. 14CCyclohexylamine injected into the caecum or colon of rats is readily absorbed and excreted in the urine. It appears that on continued intake of cyclamate the gut flora develop the ability to convert cyclamate into cyclohexylamine, which is then absorbed and excreted mainly in the urine, although a small proportion is metabolized to other compounds.

63. ANAEROBIC DEAMINATION OF CYCLOHEXYLAMINE BY INTESTINAL MICROORGANISMS IN RABBITS.

Tokieda T, Niimura T, Yamaha T, Hasegawa T, Suzuki T
Dept. Medical Chemistry, Natl. Inst. Hygienic Sciences, Kamiyoga, Setagaya-ku, Tokyo 158, Japan

Agric Biol Chem; 43(1):25-32 1979

Anaerobic metabolism of cyclohexylamine (CHA) was studied, and the role of the intestinal microorganisms in the metabolism of cyclamate (CHS) was evaluated. The effects of antibiotics on the urinary excretion of cyclohexanol (CHnol) were examined in rabbits receiving CHA orally as a 0.34% CHA-HCl soln in their drinking water. The ratio of CHnol to CHA in the urine gradually decreased with the administration of neomycin, then returned to normal after neomycin was discontinued. The addition of metronidazole (bactericidal against certain anaerobes) completely suppressed the ratio of CHnol to CHA in one rabbit while not so in the other rabbit. Cecal contents were incubated with CHA in three different media. CHnol and cyclohexanone (CHnone) formation occurred in all media and was not due to spontaneous deamination of CHA. When CHnone was incubated with cecal contents it was rapidly consumed and converted to CHnol. All the strains of microorganisms isolated from cecal contents clearly accumulated CHnone and CHnol in the medium. CHA-deaminating activity was still present in dried cells, which could be inactivated by heat treatment in boiling water for 30 min. It is suggested that CHA was anaerobically deaminated to CHnol via CHnone by anaerobes and facultative anaerobes from cecal contents of rabbits receiving CHA orally. (23 Refs)

64. METHYLGLYOXAL (MG) FORMATION IN THE METABOLISM OF XYLITOL (X) AND GLUCOSE (G) BY RAT LIVER SINGLE CELL SUSPENSION AND AS30-D AND NOVIKOFF ASCITES HEPATOMAS (MEETING ABSTRACT).

Sato J, Wang YM, Van Eys J
Univ. Texas System Cancer Center, Houston, TX, 77030

Fed Proc; 37(3):261 1978

The metabolism of methylglyoxal (MG) in 48 hr fasted SD rat liver and AS30-D and Novikoff ascites hepatoma single cell suspensions was investigated. Glyceraldehyde-3-phosphate (15 milliM) was converted rapidly to D-lactic acid (1.6 microM/mg protein/30 min) via MG (0.55 microM/mg/30 min). L-Lactic acid was formed at about one-half of the rate of D-lactic acid. Preincubation with diamide (50 milliM) plus NaF (50 milliM) in the liver cell suspension enhanced the level of MG over twofold within 30 to 60 min after addition of xylitol (X) or glucose (G) with no inhibition of alpha-ketoaldehyde dehydrogenase activity. The conversion and dilution of U-C14-X and U-C14-G to C14-MG were quantitated through MG-dinitrophenylhydrazone formation with or without the inhibitors. In the presence of inhibitors the conversion of the substrates into C14-MG was less than 0.9% from G and about 4% in X, without dilution of the specific activity in either. The studies with the ascites hepatomas demonstrated that X utilization was half that of G. X is preferentially metabolized by normal liver cells and results in an increased level of MG when compared with G.

65. METABOLIC STUDIES WITH NONNUTRITIVE SWEETENERS CYCLOOCTYLSULFAMATE AND 4-METHYLCYCLOHEXYLSULFAMATE.

Spillane WJ, Benson GA, McGlinchey G
Dept. Chemistry, Univ. College, Galway, Ireland

J Pharm Sci; 68(3):372-374 1979

The nonnutritive sweeteners cyclooctylsulfamate and 4-methylcyclohexylsulfamate were fed separately to female Wistar albino rats, and the urine was examined for the possible metabolites cyclooctylamine, cyclooctanone, cyclooctanol, 4-methylcyclohexylamine, 4-methylcyclohexanone, and cis- and trans-4-methylcyclohexanols. The av percent conversions to cyclooctylamine, cyclooctanone, and cyclooctanol were 0.127, 0.08, and 0.092, respectively. The av percent conversions to 4-methylcyclohexylamine and 4-methylcyclohexanone were 0.007 and 0.0013, respectively. No cis- or trans-4-methylcyclohexanol metabolites were found. With cyclooctylsulfamate, 42% was recovered unchanged from the urine. Cyclooctyl- and cycloheptylsulfamates were metabolized to a greater extent than cyclopentylsulfamate, which, in turn, was metabolized to a greater extent than cyclohexylsulfamate (cyclamate) and 4-methylcyclohexylsulfamate. (Author abstract) (12 Refs)

66. CONVERSION OF CYCLAMATE TO CYCLOHEXYLAMINE IN GUINEA PIGS.

Asahina M, Yamaka T, Sarrazin G, Watanabe K

Chem Pharm Bull; 20:102-108 1972

67. METABOLISM OF RADIOACTIVE LABELED XYLITOL IN RATS. (TRANSLATED TITLE)

Schmidt B, Fingerhut M, Lang K
Physiological-Chemistry Institute of the Johanannes Gutenberg University, Mainz, Germany

Klin Wschr; 42:1073-1077 1964

After feeding 14C-xylitol to rats about 60% of the label appears as respiratory 14CO(2) with a half-life time of 400 min. The half-life time of absorption is 7 +/- 1 hours. After adaptation to xylitol 70% of the label is exspired with a half-life time of 230 min, the turnover rate having raised 3 times. A similar increase in turnover rate can be observed in alloxan diabetic rats. After intravenous application of xylitol 50% is oxidized to 14CO(2) and the activity excreted in the urine is somewhat higher than after oral administration. The turnover rate in the steady state during intravenous infusion, showing the maximal capacity of the rat to oxidize xylitol, is 50 +/- 5 mg/hr and kg. Healthy animals retain 1/3 of the activity in the carcass, alloxan diabetic rats retain only 1/6 of the dose. 42-96% of the activity in the urine is found in urea. 4-6% of the activity of the administered xylitol is found in liver glycogen, less than 1% in muscle glycogen. (GER)

68. THE CONVERSION IN VIVO OF XYLITOL TO GLYCOGEN VIA THE PENTOSE PHOSPHATE PATHWAY.

McCormick DB, Touster O
Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee

J Biol Chem; 229:451-461 1957

The guinea pig converts xylitol-1-C14 to respiratory C14O(2) to an appreciable extent, a portion of the polyol apparently being excreted as such in the urine. D-Xylose-1-C14 is oxidized to C14O(2) by the rat and the guinea pig; in the latter species, most of the administered radioactivity is excreted in the urine. Xylitol is incorporated into liver glycogen at least as efficiently as is D-ribose, in both rat and guinea pig. With both xylitol and D-ribose, carbons 1 and 3 of the derived glucose contained most of the radioactivity, with carbon 1 having the greater activity. No significant differences in the pattern of labeling were observed between the rat and the guinea pig in the xylitol experiments. The findings appear to confirm enzymatic experiments which indicate that xylitol is successively converted to D-xylulose, D-xylulose 5-phosphate, and other intermediates of the pentose phosphate shunt. Implications regarding a new pathway for the metabolism of glucose, involving its conversion to D-glucuronate, L-gulonate, and the enantiomorphic forms of xylulose, are discussed.

69. INSULIN AND XYLITOL METABOLISM IN EVISCERATED RATS. (TRANSLATED TITLE)
Bassler KH, Prellwitz W
Klin Wochenschr; 42:94-95 1964

70. LACTATE FORMATION FROM SUGARS AND SUGAR ALCOHOLS IN ERYTHROCYTES. (TRANSLATED TITLE)
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Birnesser H, Reinauer H, Hollmann S
Diabetologia; 9:30-33 1973

72. MECHANISMS OF THE RENAL EXCRETION OF 2,3-DIHYDRO-3-OXOBENZISOSULFONAYOLE (SACCHARIN).
Bourgoignie JJ, Kuo H, Wang K, Pennell JP, Bricker US
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Byard JL, Golberg L
Food Cosmet Toxicol; 11:391 1973

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Collings AJ
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75. REVIEW OF THE ECONOMICS OF INDUSTRIAL PRODUCTS WITH REFERENCE TO THE GLUCOSE, FRUCTOSE, SORBITOL AND XYLITOL METABOLISM AND ITS THERAPEUTIC APPLICATION. (TRANSLATED TITLE)
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Grutte FK, Rodel H
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80. CARBOHYDRATE METABOLISM: CONTROL AND PHYSIOLOGICAL SIGNIFICANCE. III. XYLITOL METABOLISM AND PHYSIOLOGICAL EFFECT. (TRANSLATED TITLE)
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81. STUDIES ON SYNTHETIC SWEETENING AGENTS. XVI. METABOLISM OF SODIUM CYCLAMATE. 5. THE METABOLISM OF SODIUM CYCLAMATE IN RABBITS AND RATS AFTER PROLONGED ADMINISTRATION OF SODIUM CYCLAMATE.
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Chem Pharm Bull; 20:1093-1101 1972

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Lang K
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Chem Pharm Bull; 20:1351 1972

90. CONVERSION OF CYCLAMATE TO CYCLOHEXYLAMINE IN RATS.
Oser BL, Carson S, Vogin EE, Sonders RC
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Parekh C, Goldberg EK, Golberg L
Toxicol Appl Pharmacol; 17:282 1970

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Pitkin RM, Andersen DW, Reynolds WA, Filer LJ
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Stein G
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Chem Pharm Bull; 20:1357-1361 1972

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III. SHORT-TERM TOXICITY, SHORT-TERM TUMORIGENICITY AND OTHER BIOCHEMICAL STUDIES

97. SHORT-TERM TOXICITY OF CYCLOHEXYLAMINE HYDROCHLORIDE IN THE RAT.
Gaunt IF, Sharratt M, Grasso P, Lansdown AB, Gangolli SD
British Ind. Biol. Res. Assoc., Surrey, England
Food Cosmet Toxicol; 12(5/6):609-624 1974

The effects on CFE strain rats of short term exposure to cyclohexylamine hydrochloride (CHA) were studied. Groups of 15 male and 15 female rats were given diets containing 0 (control), 600, 2000 or 6000 ppm CHA for 13 wk. No changes in the hematological examinations, serum analyses or urinary cell excretion values were associated with CHA treatment. At the 2 higher dosage levels there was a reduced rate of body-wt gain and food intake. Paired feeding showed that the reduced food intake did not fully account for the failure to gain wt. The absorption of nutrients was normal but measurements of oxygen consumption suggested that an increased basal metabolic rate might account, in part, for the failure to gain wt. The renal concentrating ability was slightly reduced in the females given the highest dietary concentration of CHA. The wt of most of the organs were lower in the rats given diets containing 2000 or 6000 ppm CHA was this was related to the reduced body wt. The testis wt and relative testis wt were reduced and histopathological examination showed reduced spermatogenesis. However, the rats remained fertile and there was no evidence of abnormalities in their offspring. Apart from the effects on the testis, no changes were seen in the histopathological examination. The no-untoward-effect level established in this study was 600 ppm, a level equivalent to an intake of approximately 30 mg CHA/kg/day. It is concluded that CHA causes no adverse effects in rats over a 90-day period at 600 ppm in the diet, but that at 2000 or 6000 ppm it reduces the rate of body wt gain as well as food intake.

98. SOME EFFECTS OF DIET ON CYCLAMATE TOXICITY (MEETING ABSTRACT).
Pritchard AB, Warner RG
Cornell Univ, Ithaca, NY 14853
Fed Proc; 36(3):1117 1977

Ingested calcium cyclamate (CYC) was poorly absorbed and toxic to weanling rats fed a low-residue semi-synthetic diet but not to those fed a stock diet as measured by survival and weight gain after 14 days of feeding (Ershoff, P S E B M, 141, 857 (1972)). This study investigated the contribution of diarrheal stress to CYC toxicity in rats fed low-residue diets. Feeding 5% CYC in a low-residue diet (24% casein, 63% sucrose, 5% corn oil, vitamins, minerals, no fiber) produced severe diarrhea, weight loss and 67% lethality within 14 days. Feeding 8.5% Na2SO4 or 30% lactose in the low-residue diet also produced severe diarrhea but only slight growth depression and no deaths. Incorporating lactose at 0, 15 and 30% with CYC at 0, 1, 2.5 or 5% in the low-residue diet increased diarrhea and reduced weight gain and survival in a dose-related fashion. CYC lethality, after single IP administration, was greatest in rats with diarrhea induced by prefeeding 30% lactose in the low-residue diet for 6 days and similar in rats prefed the low-residue and stock diets. It appeared that 1) the stress of osmotic diarrhea, only slightly detrimental to growth but not lethal, increased susceptibility to CYC intoxication and 2) no difference in CYC toxicity was seen between low-residue and stock diet-fed rats with a non-oral route of CYC administration. (Author Abstract)

99. PROTECTIVE EFFECTS OF CHOLESTYRAMINE IN RATS FED A LOW-FIBER DIET CONTAINING TOXIC DOSES OF SODIUM CYCLAMATE OR AMARANTH.
Ershoff BH
Inst. Nutritional Studies, Culver City, CA 90230
Proc Soc Exp Biol Med; 152(2):253-256 1976

Immature male Sprague-Dawley rats were fed a purified, low-fiber diet containing massive doses of sodium cyclamate or amaranth. Sodium cyclamate, when incorporated at a 5% level in the purified, low-fiber diet, resulted in toxic manifestations that were counteracted by the concurrent dietary administration of cholestyramine at a 2 1/2% level. Other anion exchange resins were also active. Cholestyramine at a 2 1/2% level of supplementation was also active in counteracting the toxic effects induced by amaranth when the latter was incorporated at a 5% level in the purified, low-fiber diet. (6 refs)

100. SYNERGISTIC TOXICITY OF FOOD ADDITIVES IN RATS FED A DIET LOW IN DIETARY FIBER.
Ershoff BH
Inst. Nutritional Studies, Culver City, CA 90230
J Food Sci; 41(4):949-951 1976

Data are presented indicating that some food additives have a synergistic toxic effect when incorporated in a purified, low-fiber diet at dosages that have little if any adverse effect when fed individually. Immature male Sprague-Dawley rats (average initial body wt 50.4 g) were fed a purified, low-fiber diet to which were added supplements of 2% sodium cyclamate, 2% FD and C Red No. 2 (amaranth), and 4% polyoxyethylene (20) sorbitan monostearate (Tween 60) individually or in combination. Although supplements of any one of the three food additives had little if any deleterious effect, combined supplements of sodium cyclamate and FD and C Red No. 2 resulted in a marked retardation in weight gain, an unhealthy appearance of the fur, alopecia, and extensive diarrhea with watery and mushy stools. Concurrent administration of all three food additives resulted in a further retardation in weight gain and death of all test animals within 14 days. The deleterious effects obtained on the latter diet could be largely counteracted by the concurrent administration of various dietary fiber-containing materials. Blond psyllium seed powder was particularly potent in this regard. The protective factor or factors in the powder were distinct from any of the known nutrients and from cellulose per se. The observation that some food additives have a cumulative or synergistic effect when incorporated in a purified, low-fiber diet may be of considerable public health significance.

101. MODIFICATION BY FIBER OF TOXIC DIETARY EFFECTS.

Kritchevsky D
Wistar Inst. Anatomy and Biology, Philadelphia, PA 19104
Fed Proc; 36(5):1692-1695 1977

Studies of the influence of diet on the response of rats and mice to carcinogens, toxic chemicals, and infectious agents are summarized. Increases in dietary fiber had a protective effect against x-irradiation and dietary 2-acetylaminofluorene, 2,5-di-t-butylhydroquinone, cadmium, sodium cyclamate, amaranth, and nonionic surface active agents. However, fiber did not protect animals against pneumococcal infection or the hepatomegalic effects of ethyl-p-chlorophenoxyisobutyrate. (17 Refs)

102. TESTICULAR EFFECTS OF CYCLOHEXYLAMINE HYDROCHLORIDE IN THE RAT.

Mason PL, Thompson GR
British Industrial Biological Res. Assn., Woodmansterne Road, Carshalton, Surrey SM5 4DS, England
Toxicology; 8(2):143-156 1977

The role of food restriction in the etiology of the testicular lesions associated with cyclohexylamine hydrochloride (CHA) administration was investigated in Wistar and Sprague-Dawley rats. Groups of 25 rats were fed diets containing 6,000, 2,000 and 600 ppm CHA for 90 days. Ad lib, pair-fed and paired-wt control groups were used. Rats fed diets containing 6,000 and 2,000 ppm CHA showed significant decreases in food consumption, body wt and body wt gain. Significant increases in the incidence of testicular lesions were found only in those animals fed 6,000 ppm CHA. The no-effect level for significant testicular changes was between 2,000 and 6,000 ppm. Absence of a similar incidence of lesions in either the paired-wt or pair-fed control groups indicated that inanition was not primarily responsible for the development of the lesions. The toxicological significance of these findings is discussed. (10 Refs)

103. EFFECTS OF CYCLAMATE CALCIUM ON THE IMMUNE RESPONSE IN RABBITS.

Hampton CM, Myers RL
Dept. Life Sciences, Southwest Missouri State Univ., Springfield, Mo. 65802
Arch Environ Health; 131(1):51-53 1976

To determine the effect of cyclamate calcium on the humoral immune response in rabbits, 5 rabbits were given a 3% and 5 rabbits were fed a 5% water soluble ad libidum of cyclamate calcium. A 3rd group served as controls. After 150 days, the animals were tested for their ability to respond immunologically to bovine serum albumin (BSA). Other aspects of immunity investigated were the presence or absence of neoplasia of the urinary bladder, spleen, thymus, and lymph nodes, the number of WBC and RBC, and cyclamate conversion and excretion in the urine. The results indicated that the 5% group had a delayed and suppressed response to BSA. No neoplasia was detected. This group had fewer RBC and excreted increased concentrations of cyclohexylamine in the urine. Because current research suggests that many tumors might arise as a result of a failure of the immune response to recognize neoplastic cells, the authors conclude that cyclamate suppression of the antibody response may retard the tumor surveillance function of the immune system.

104. PHYSIOCHEMICAL AND OTHER FACTORS DETERMINING LOCAL SARCOMA PRODUCTION BY FOOD ADDITIVES.

Grasso P, Gangolli SD, Golberg L, Hooson J
Brit. Indust. Biol. Res. Ass., Carshalton, Surrey, England
Food Cosmet Toxicol; 9(4):463-478 1971

It was found previously that repeated sc injections of water-soluble food colorings and other selected compounds into rats causes reactions dependent on the lipophilic properties of the injected substances. These reactions were divided into four classes: Type I was a mild reaction in connective tissue; Type II was called a moderately severe reaction and was also limited to connective tissue; a Type III reaction consisted of intense macrophage response; and a Type IV reaction was characterized by the local deposition of collagen and fibroblastic proliferation. These reactions are considered in this study as an indicator of possible tumor production caused by food additive agent injections into rats. Physicochemical studies were done on the agents to be injected-the food additives Blue VRS, Patent Blue V, Tween 80, and sodium and calcium salts of cyclohexylsulfamic acid. Shell or Carworth albino rats of strain E were than subjected to sc biweekly injections of these agents. Calcium cyclamate caused a Type IV reaction in connective tissue with subsequent formation of local sarcomas, while sodium cyclamate showed no tissue destruction and no tumorous growths. Tween 80 caused a Type III tissue reactions, with tumor formations occurring in half the injected animals. Blue VRS and Patent Blue V both showed Type IV destruction of the tissue and both had a considerable influence on local tumor production. All the tumors that developed were found to be fibrosarcomas, ranging from well differentiated forms to poorly differentiated structures. The development of local tumors was prevented, however, when test compounds were given in relatively dilute solutions. A correlation appeared between the progressively intensifying lesion induced in the short-term tests and the eventual development of sarcomas. Physicochemical factors, unrelated to any specific chemical structure, determine both the tissue reaction and the ultimate evolution of sarcomas. In the authors' discussion the observations are finally examined in the light of previous publications.

105. PRODUCTION OF MOUSE URINARY BLADDER CARCINOMAS BY SODIUM CYCLAMATE.

Bryan GT, Erturk E
U. Wisconsin Med. Sch., Madison, Wisconsin
Science; 167(3920):996-998 1970

Pellets of pure cholestrol or sodium cyclamate suspended in cholesterol were surgically placed in the bladder lumens of duplicate groups of 100 female Swiss mice, 60-90 days old. By 6.6 hr, 99% of the sodium cyclamate eluted from the pellets. The first bladder carcinoma was seen in a cyclamate-fed mouse, 229 days after surgery. The mice exposed to cyclamates had a higher incidence of bladder carcinomas (78 and 61% as opposed to 12 and 13% in the controls); the carcinomas were more often multiple, invasive, and had a high degree of mitotic activity.

106. PRODUCTION OF URINARY BLADDER CARCINOMAS IN MICE BY SODIUM SACCHARIN.

Bryan GT, Erturk E, Yoshida O
U. Wisconsin Med. Sch., Madison
Science; 168(3936):1238-1240 1970

Pellets of sodium saccharin (NaS; 20%) and cholesterol (pellet wt.=20-24 mg) were implanted in the bladder lumens of 60-90-day-old female Swiss mice and their rate of disappearance measured. The bladder lumens of groups of 100 mice were implanted with either pure cholesterol or NaS +

cholesterol (1:4) and bladder carcinomas of animals surviving more than 175 days examined and classified according to infiltration. By 5.5 hours, 50% of the saccharin in the bladder disappeared and 99% was eluted from the pellets by 1.5 days. Frequency of bladder carcinomas was 47% and 52% for NaS-treated mice in comparison to 13% and 12% for controls (cholesterol alone). Tumors were often multiple with high mitotic activity and pleomorphism. Other tissues of the mice responded to the NaS as did controls. Mouse bladder response to NaS is considered more severe than it is to sodium cyclamate.

107. TEST FOR CARCINOGENICITY OF FOOD ADDITIVES AND CHEMOTHERAPEUTIC AGENTS BY THE PULMONARY TUMOR RESPONSE IN STRAIN A MICE.

Stoner GD, Shimkin MB, Kniazeff AJ, Weisburger JH, Weisburger EK, Gori GB
Sch. Med., U. California, San Diego
Cancer Res; 33(12):3069-3085 1973

Forty-one food additives and 20 chemotherapeutic agents were examined for their ability to induce primary lung tumors in A mice. The animals received ip injections of each compound for 8 wk and were killed 24 wk after the first injection. With some of the more toxic compounds, fewer injections were administered. Two or three dose levels were used for each chemical. Cinnamyl anthranilate was the only agent of the 41 food additives tested which induced primary lung tumors. Safrole and sodium saccharin were negative for pulmonary tumor response under the conditions used. Of the 20 chemotherapeutic agents, including alkylating chemicals, 12 were found to be positive in inducing pulmonary tumors: uracil mustard, thio-TEPA, estradiol mustard, dibenzyline, pyrimethamine, 5-azacytidine, beta-deoxythioguanosine, isophosphamide, 1-propanol-3,3'-imino-dimethanesulfonate, phenesterin, imidazole mustard, and dapsone. Uracil mustard was the most active compound. Myleran was inactive at the dose levels used.

108. EFFECTS OF SACCHARIN ON RENAL TUBULAR TRANSPORT OF ORGANIC IONS IN ADULT FEMALE RATS (MEETING ABSTRACT).

Goldstein R, Hook JB, Bond JT
Mich State Univ, East Lansing, MI 48824
Fed Proc; 36(3):1116 1977

Previous investigations examining the metabolism of the non-nutritive sweetener, saccharin (2,3 dihydro-3-oxobenzisosulfanazole), have suggested that this compound is rapidly excreted in its unmetabolized form in the urine. No definitive information concerning the mechanism of the renal excretion of saccharin has been reported. Based on the chemical structure of the parent compound and its hydrolysis products, it was hypothesized that saccharin would influence renal tubular transport. The purpose of these experiments was to determine its effects on renal tubular transport systems for organic anions in adult female rats. The ability of renal cortical slices to actively accumulate p-aminohippurate (PAH) was used as an index of organic anion transport capacity. Slices were incubated in Cross-Taggart medium, containing .112M, .224M, .449M or .897 M concentrations of saccharin for 90 min at 25 degrees C in 100% O2 and slice/medium (S/M) ratios were determined. PAH S/M ratios significantly decreased at the increased concentrations, suggesting competitive inhibition. To determine the specificity of this effect, uptake of a prototype organic base, N-methylnicotinamide (NMN), was quantified. Base transport was similarly depressed at higher concentrations of saccharin. These results support the hypothesis that saccharin influences renal tubular transport by an undefined mechanism, possibly metabolic and/or competitive. (Author Abstract)

109. SACCHARIN DOES NOT BIND TO DNA OF LIVER OR BLADDER IN THE RAT.

Lutz WK, Schlatter C
Inst. Toxicology, Federal Inst. Technology, CH-8063, Schwerzenbach, Switzerland
Chem Biol Interact; 19(2):253-257 1977

The binding of saccharin to the liver and bladder DNA of two male Sprague-Dawley rats given 372 or 390 mg/kg saccharin by gavage was investigated. The percentage of saccharin recovered in the first urine fraction was 66% and 84%, total recovery of radioactivity from urine, feces, and cage rinse (animals were killed 50 hr after administration) was 93% and 102%. Radioactivity measurements of DNA isolated from the liver and bladders indicated no incorporation of saccharin. Any binding that does occur is less than 1 molecule/10^8 nucleotides in the liver and less than 1 molecule/10^7 nucleotides in the bladder. This minimal binding of saccharin is compared to that of N-N-dimethylnitrosamine and benzo(a)pyrene. (16 Refs)

110. COVALENT BINDING OF WEAK CHEMICAL CARCINOGENS SUCH AS BENZENE, ESTRONE, ETHINYLESTRADIOL AND SACCHARIN TO DNA OF RAT LIVER IN VIVO (MEETING ABSTRACT).

Lutz WK, Jaggi W, Schlatter C
Inst. Toxicology, Federal Inst. Technology, 8603 Schwerzenbach, Switzerland
Proc Am Assoc Cancer Res; 19:13 1978

Weak carcinogens cannot be detected in long-term studies unless extremely high doses are used. Binding of such compounds to DNA in an animal, however, can still be measured with radiotracers. We administered radiolabeled suspected carcinogens to adult rats, purified DNA from the liver and were able to measure DNA-bound radioactivity from all compounds except saccharin, where the gross count of the DNA sample was within the variability of our background (0.7 cpm as one standard deviation). The table summarizes averaged results for the compounds benzene, estrone, ethinylestradiol and saccharin, indicating the label, total dose, disintegration per min (dpm)/mg DNA and the binding index. The binding index is defined as binding to DNA/dose, ie, dpm per mg DNA/dpm per kg, and the limit of detection is dependent on the yield of DNA from a specific organ per kg body wt, the net radioactivity on the purified DNA and the total dpm administered. Typical liver carcinogens (N,N-dimethylnitrosamine or aflatoxin B1) give rise to a binding index on the order of 10**-5 to 10**-4 and a comparison with our limit of detection, reached with saccharin, shows that the binding of a suspected compound to DNA could well serve as a mammalian screening method for the detection of weakest carcinogenicities.

111. SACCHARIN INHIBITS GUANYLATE CYCLASE ACTIVITY: POSSIBLE RELATIONSHIP TO CARCINOGENESIS.

Vesely DL, Levey GS
Dept. Medicine, Univ. Miami Sch. Medicine, Miami, FL, 33152
Biochem Biophys Res Commun; 81(4):1384-1389 1978

The effect of saccharin (2,3-dihydro-3-oxobenzisosulfonazole) on guanylate cyclase activity was tested in a variety of tissues obtained from male Sprague-Dawley rats. Saccharin significantly inhibited guanylate cyclase in urinary bladder, liver, stomach, colon, and kidney tissues over the concentration range 16-160 mM. Maximum inhibition was 60%-75%. The concentrations of saccharin decreasing guanylate cyclase activity in the in vitro rat urinary bladder assay (approx 3 to 9 mg/ml), were well within the range of concentration which can be obtained from the urine

of persons using low calorie soft drinks and sugar substitutes which can interact in vivo with bladder tissue. The saccharin used in this study was synthesized by the Maumee process and contained no detectable amounts of o-toluenesulfonamide, the impurity most often associated with cancer. It is concluded that the question of saccharin carcinogenicity in man must be seriously studied regardless of its mode of synthesis. (29 Refs)

112. OXALATE FORMATION FOLLOWING XYLITOL INFUSION IN 4-DEOXYPYRIDOXINE TREATED RABBITS.

Oshinsky RJ, Wang YM, Van Eys J
Pediatrics Department, The University of Texas Cancer System Center, Houston, Texas 77025
Fec Proc; 35:419 1976

Oxalate (OX) crystals were reported to accumulate in kidneys of patients who expired after Xylitol (X) administration (Thomas, et al, Med. J. Aust. 1:1238, 1972). We have shown previously that this was not a primary effect of X in normal or oxythiamine treated rabbits (Wang, et al, Fed. Proc., 35:920, 1975). I.P. injection of 300 mg/kg 4-Deoxypyridoxine (DP) in rabbits caused the EGOT and EGPT activity index to increase 1.5 and 1.37 fold respectively at 6 hrs. post injection. While SGOT levels remained normal, 3 of 11 rabbits had convulsions and subsequently died. X in a 25% solution at 2 gm/kg was infused in normal and DP-treated, fasted rabbits. A small increase in plasma OX from 20 to 60 ug/ml was observed 30 mins. following X infusion in both groups. Urinary OX levels remained normal. No significant difference was seen in either plasma or urinary OX levels between the groups. Plasma X retention time was similar in both groups. Glucose, at an equivalent dose in DP-treated animals, resulted in higher plasma OX levels than X. X administered orally (5 g/kg) to DP-treated animals gave no urinary OX rise. The infusion of 14C-X (2 g/kg) in a DP-treated rabbit (300 mg/kg) showed that the rate of conversion of 14C-X to 14C-OX is minimal. Therefore, our experimental findings suggest no relationship between OX accumulation and X toxicity.

113. AN INVESTIGATION OF OXALATE FORMATION FROM XYLITOL INFUSION IN RABBITS.

Wang TM, Oshinsky RJ, Lantin E, Van Eys J
Department of Pediatrics, M.D. Anderson Hospital and Tumor Institute, the University of Texas System Cancer Center, Houston, Texas 77025
Fed Proc; 35:920 1975

Recently we have proposed the potential use of xylitol (X) in the treatment of glucose 6-phosphate dehydrogenase deficiency. However, sporadic reports of X toxicity have appeared after rapid infusion of high dose hypertonic X solutions. In addition to liver toxicity, oxalate crystals were reported to accumulate in kidneys of patients who expired after X administration (Thomas, et al., Med. J. Aust. 1:1238, 1972). Transient thiamine deficiency was induced in rabbits by intraperitoneal administration of oxythiamine (OT) in varying doses. OT at a dose of 20 mg/kg in a single injection showed five fold increase in pyruvate and lactate ratio and a 12% decrease of erythrocytic transketolase activity. SGOT levels remained normal. X in a 25% solution at 2 gm/kg was infused in normal and OT treated, fasted rabbits. A transient but modest increase in plasma oxalate was observed in both groups. The urinary oxalate levels remained normal. There was no significant difference of plasma or urinary oxalate level between the groups. More severe liver toxicity was found in X-OT treated animals, and plasma X retention time was longer. Glucose, at an equivalent dose, resulted in higher plasma oxalate levels than X. We find therefore no experimental evidence for a relation between oxalate accumulation and X toxicity.

114. THE EFFECTS OF SODIUM CYCLAMATE ON THE GROWTH OF CHLAMYDOMONAS REINHARDI (WILD TYPE).

Mineo L, Figley WK, Majumdar SK
Dept. Biology Lafayette Coll., Easton, PA 18042
Proc Pa Acad Sci; 49(2):103-106 1975

The results of growth experiments showed inhibition of population growth for the green algae, Chlamydomonas reinhardi (wild type-) corresponding to the amount of sodium cyclamate in the culture medium. Some inhibition of growth occurred at 0.00001% (0.1 ppm) cyclamate with increased inhibition at higher concentrations up to 0.1% (1,000 ppm). The effect of cyclamate on the growth curve of C reinhardi was delayed. As cells in the logarithmic phase of growth were used as inocula for growth curves, the primary effect of cyclamate was neither the onset of a lag phase nor a decrease in logarithmic growth rate, but a decrease in total cell crop. Both the chlorophyll content and cyclohexylamine (an injurious metabolite of cyclamate) content of cultures were assayed to explain this type of growth inhibition. There were no significant differences in the chlorophyll content of control and experimental populations. Results from chromatographic studies also showed that cyclohexylamine is not likely to play a role in curbing population growth in C reinhardi. (30 refs)

115. BIOLOGICAL ACTIVITY OF SACCHARIN AND CYCLAMATES IN GOLDEN HAMSTERS.

Adkins A, Hupp EW, Gerdes RA
Tex J Sci; 23:575 1972

116. COMPLEX FORMATION BETWEEN MACROMOLECULES AND DRUGS. VIII. BINDING OF SACCHARIN, N-METHYL SACCHARIN, AND THE DIURETIC DRUGS HYDROFLUMETHIAZIDE AND BENDROFLUMETHIAZIDE TO HUMAN SERUM ALBUMIN.

Agren A, Back T
Acta Pharm Suec; 10:223-228 1973

117. MYOCARDIAL LESIONS: A REASSESSMENT OF THE TOXICOLOGY OF CALCIUM CYCLAMATE.

Bajusz E
Nature (Lond); 223:406-407 1969

118. THE SAFETY OF ORAL XYLITOL

Brin M, Miller ON
Sugars in Nutrition. Sipple HL, McNutt KW, ed. Academic Press, 1974.

119. SYMPATHIOCOMIMETIC EFFECTS OF CYCLOHEXYLAMINE.

Classen HG, Marquardt P, Spath M
Arzneim Forsch; 18:590-594 1968

120. BIOCHEMISTRY OF CARBOHYDRATES IN PARENTERAL NUTRITION. (TRANSLATED TITLE)

Ferster H, Hoffman H
Infusiotherapie; 1:265-279 1973

121. ON THE ACTION OF THE SWEETENER CYCLAMATE ON LIVER PARENCHYMA, CORRESPONDING ENZYMES AND BLOOD COAGULATION FACTORS. (TRANSLATED TITLE)

Gottinger E, Hagmuller K, Hellauer H, Vinazzer H
Wien Klin Wochenschr; 80:328-332 1968

122. NEW HISTOLOGICAL FINDINGS AND FURTHER EXPERIMENTAL DATA ON CYCLAMATE TOLERANCE IN GUINEA PIGS. (TRANSLATED TITLE)

Hagmuller K, Hellauer H, Winkler R, Zangger J
Wein Klin Wochenschr; 81:927-938 1969

123. THE ANTIKETOGENIC EFFECTS OF POLYHYDRIC ALCOHOLS IN RAT-LIVER SLICES.
Haydon RK
Biochim Biophys Acta; 46:598-599 1961

124. EFFECTS OF INTRAVENOUS INJECTION OF XYLITOL ON PLASMA INSULIN.
Hirata Y, Fujisawa M, Ogushi T
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125. EFFECTS OF INTRAVENOUS INJECTION OF XYLITOL ON BLOOD SUGAR, BLOOD PYRUVIC ACID AND PLASMA INSULIN LEVELS IN THE DOG.
Hirata Y, Fujisawa M, Sato H, Asano T, Katsuki S
Z Klin Chem Klin Biochem; 145:111-119 1968

126. XYLITOL EFFECT ON KETOGENESIS IN ALLOXAN DIABETIC RAT LIVER SLICE.
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127. MECHANISM OF THE LAXATIVE EFFECT OF SODIUM SULFATE, SODIUM CYCLAMATE AND CALCIUM CYCLAMATE.
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128. EFFECTS OF 14C-XYLITOL, GIVEN INTRAVENOUSLY, ON THE SERUM GLUCOSE, INSULIN AND LIPID CONCENTRATIONS OF MALE AND FEMALE BABOONS.
Jourdan MH, McDonald J, Henderson JR
Nutr Metab; 14:92-99 1972

129. SUBACUTE TOXICITY STUDIES WITH SODIUM SACCHARIN AND TWO HYDROLYTIC DERIVATIVES.
Kennedy GL, Fancher OE, Calandra JC
Toxicology; 6:133-138 1976

130. PLASMA INSULIN RESPONSE TO INTRAVENOUSLY ADMINISTERED XYLITOL IN DOGS.
Kuzuya T, Kanazawa Y, Kosaka K
Metabolism; 15(12):1149-1152 1966

131. STIMULATION OF INSULIN SECRETION BY XYLITOL IN DOGS.
Kuzuya T, Kanazawa Y, Kosaka K
Endocrinology; 84:200-207 1969

132. NUTRITIONAL TRIALS WITH AND WITHOUT SACCHARIN, STUDY OF MINIMAL TOXICITY. (TRANSLATED TITLE)
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133. SUGARS IN PARENTERAL NUTRITION.
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134. PHARMACOLOGICAL CHARACTERISTICS OF CYCLOHEXYLAMINE, ONE OF METABOLITES OF CYCLAMATE.
Miyata T, Kase Y, Kamidawa Y, Kataoka M, Kikuchi K, Touchi T
Lif Sci; 8:843-853 1969

135. PENTITOLS AND THE MECHANISM OF INSULIN RELEASE.
Montague W, Howell SL, Taylor KW
Nature (Lond); 215:1088-1089 1967

136. THE INFLUENCE OF XYLITOL AND OTHER POLYOLS AND SUGARS ON FAT MOBILIZATION.
Opitz K
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137. MEASUREMENTS OF COMPARATIVE ACTIVITY OF THE ENZYMES OF THE GLUCURONIC ACID - XYLULOSE CYCLE IN THE LIVER, IN THE EPIDIDYMAL FAT TISSUE OF THE RAT AND IN A MORRIS HEPATOMA AND A FIBROCYTE CULTURE. (TRANSLATED TITLE)
Petrich Ch, Reinauer H, Hollmann S
Z Klin Chem Klin Biochem; 10:355-358 1972

138. GROWTH INHIBITORY ACTION OF SACCHARIN AND CYCLAMATE ON RATS RECEIVING A POOR RICE DIET.
Sabri MI, Sharma SK, Krishna Murti CR
Br J Nutr; 23:505-509 1969

139. EFFECT OF XYLITOL ON TESTICULAR PROTEIN AND RNA BIOSYNTHESIS OF RATS.
Shima S, Mitsunaga M, Nakao T
Endocrinol Jpn; 17:283-287 1970

140. EFFECT OF DIETARY POLYOLS ON SERUM CHOLESTEROL IN RATS.
Staub HW, Thiessen R
Fed Proc; 31:391 1972

141. HYPOGLYCEMIC EFFECTS OF SACCHARIN IN EXPERIMENTAL ANIMALS.
Thompson MM, Mayex J
Am J Clin Nutr; 7:80 1972

142. PARENTERAL NUTRITION.
Touster O
Proceedings on an International Symposium, Vanderbilt University, School of Medicine, Nashville. Meng HC, Law DH, Thomas CC, ed. Springfield, Illinois, pp. 131-138, 1970.

143. ARE THERE DIFFERENCES BETWEEN THE ANTIKETOGENIC ACTION OF COMMON SUGARS AND POLYALCOHOLS? (TRANSLATED TITLE)
Wagner G, Bassler KH
Med Ernaehr; 12:53-54 1971

144. PLASMA INSULIN CONCENTRATIONS IN DOGS AND MONKEYS AFTER XYLITOL, GLUCOSE OR TOLBUTAMIDE INFUSION.
Wilson RB, Martin JM
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145. HEPATIC METABOLISM OF PENTITES.
Woods HF
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Woods HF, Krebs HA
Biochem J; 134:437-443 1973

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Yamamura HI, Lee IP, Dixon RL
J Pharm Sci; 57:1132-1134 1968

IV. LONG-TERM TOXICITY AND TUMORIGENICITY STUDIES

148. A CARCINOGENICITY STUDY OF COMMERCIAL SACCHARIN IN THE RAT.

Munro IC, Moodie CA, Krewski D, Grice HC
Bureau Chemical Safety, Health Protection Branch, Ottawa, Canada
Toxicol Appl Pharmacol; 32(3):513-526 1975

The carcinogenicity of commercial saccharin was investigated in rats. Groups of 60 male and 60 female Charles River rats were fed diets containing sodium saccharin to provide daily doses of 0, 90, 270, 810, or 2,430 mg saccharin/kg/day. The animals were treated for a period of 26 mo. Food consumption, body weight, and clinical examinations were conducted weekly on all rats. The animals were free of the bladder parasite Trichisomoides crassicauda. Four bladder tumors were found in treated animals: one male and one female from the 90-mg/kg group and two males given 810 mg/kg. The tumors were transitional cell papillomata, none of which were invasive. Three bladder calculi were observed grossly and several others were noted in urine samples examined microscopically. The presence of bladder calculi was associated with neither saccharin treatment nor with the presence of bladder tumors. Saccharin administration thus does not appear to be accompanied by an increase in tumor incidence, although high doses were associated with reduced body weight in both sexes and decreased longevity in male rats.

149. CANADIAN SACCHARIN STUDY (LETTER TO EDITOR).

Arnold DL, Moodie CA, Stavric B, Stoltz DR, Grice HC, Munro IC
Health Protection Branch, Health and Welfare Canada, Ottawa, Ontario, Canada KIA 0L2
Science; 197(4301):320 1977

Corrections and comments on a news article on the "Canadian Saccharin Study" are offered. Neither lot of saccharin used in the study contained detectable O-toluenesulfonamide and no Trichosomoides crassicauda or their ova were found in the bladders. The incidence of microcalculi in the rats' urine was not related to saccharin treatment. Mutagenicity testing was also discussed. (4 Refs)

150. SACCHARIN AND CANCER (LETTER TO EDITOR).

Homburger F
Bio-Res. Inst., Inc., Cambridge, MA 02141
N Engl J Med; 297(10):560-561 1977

The validity of the Canadian study on saccharin is questioned because bladder lesions in rats may be caused by Trichosomoides crassicauda, as well as by natural carcinogens in food or hormonal imbalance. Further studies should be performed on other species (eg, hamsters) that are susceptible to bladder carcinogens known to affect humans (eg, beta-napthylamine). (2 Refs)

151. COMBINED CHRONIC FEEDING AND THREE-GENERATION REPRODUCTION STUDY OF SODIUM SACCHARIN IN THE RAT (MEETING ABSTRACT).

Taylor JM, Friedman L
Food and Drug Admin., Washington, DC
Toxicol Appl Pharmacol; 29(1):154 1974

The carcinogenic and reproductive effects of sodium saccharin were studied in Charles River CD rats in a combined chronic and three-generation reproduction study. For the chronic study, 48 male and 48 female F1 a weanling offspring per test group were selected and continued on the same test regimen as their parents. The dietary levels were 0, 0.01, 0.1, 1.0, 5.0 and 7.5% sodium saccharin. Calcium cyclamate was fed as a reference compound at 5.0%. The rats were mated to produce two litters. Serial sacrifices were performed at 14 and 18 mo. The study was continued until the number of survivors in a group fell to 20% of the starting number. The last rats were killed approximately 28 mo after the first weanlings were selected for the chronic study. There were no significant differences between test and control groups in hematological values, organ weights or survival. Average weaning weights were decreased in litters from parents receiving 5 and 7.5% sodium saccharin and 5% calcium cyclamate; other reproductive indices showed scattered variations, but these were not consistent for all generations. During the chronic study some of the initial weaning weight depression was overcome, but rats on 5 and 7.5% sodium saccharin and 5% calcium cyclamate had lower average body weights throughout the study. Histopathological examination of the urinary bladders from rats on the chronic study longer than 18 mo revealed an increased incidence of transitional cell carcinomas in the 7. 5% sodium saccharin group.

152. RESPONSE OF THE RAT TO SACCHARIN WITH PARTICULAR REFERENCE TO THE URINARY BLADDER.

Chowaniec J, Hicks RM
Sch. Pathology, Middlexex Hosp. Medical Sch., London, England
Br J Cancer; 39(4):355-375 1979

Male and female Wistar rats were administered sodium saccharin for life (2 yr), either in their drinking water or diet. The max palatable saccharin dose in the drinking water was 2 g/kg/day and, even then, there was some voluntary restriction of fluid intake in the males. By contrast, 4 g/kg/day was palatable in the diet. Control rats of both sexes received saccharin-free diets and drinking water. Mild urothelial hyperplasias developed by 85 wk in rats of both sexes receiving saccharin in drinking water or diet; the incidence was statistically significant in both the bladders and kidneys of rats receiving the higher dose in the diet, but only in the kidneys of rats receiving the lower dose in the drinking water. Telangiectasia of the vasa recta was significant in saccharin-treated rats of both sexes at both doses. Of the three bladder tumors, that were seen at 95 or 102 wk, all were in males receiving the higher saccharin dose in the diet. No consistent relationship between bladder epithelial hyperplasias and crystalluria could be demonstrated, although all three bladder tumors were associated with some form of mineralisation. The results suggest a particular susceptibility of males to saccharin treatment. However, rather than initiating carcinogenesis, saccharin may promote or enhance the development of latent tumor cells. (78 Refs)

153. LONG-TERM SAFETY EVALUATION AND METABOLISM OF O-BENZOIC SULFIMIDE (SACCHARIN) IN RHESUS MONKEYS.

Coulston F, McChesney E, Benitz KF
Inst. Comparative and Human Toxicology, Albany Medical Coll., Albany, NY, 12208
Ecotoxicol Environ Saf; 2(1):33-48 1978

The results of a 79-mo safety evaluation of saccharin in 7 male and 7 female monkeys are reported. Saccharin was administered by stomach tube 6 days/wk at daily doses of 20 mg/kg (4 animals), 100 mg/kg (4 animals), and 500 mg/kg (6 animals). Six monkeys of comparable age and wt served as controls. Although there were five deaths, one in each treatment group and two in the control group, none of the deaths was related to saccharin intake. The dose regimens had no effect on animal growth or on serum biochemical or whole blood hematological parameters. At necropsy, the only lesions detected grossly or microscopically occurred as frequently in

controls as in any of the treated groups. Moreover, the suspected target organ, the urinary bladder, was free of lesions in all groups. Metabolic experiments demonstrated that saccharin was eliminated rapidly (estimated half-life of 9.5 hr), mostly in the urine, and in at least 98% unchanged form. It is concluded that the no-effect level of saccharin for the rhesus monkey exceeds 500 mg/kg/day, a dose that, on a wt basis, is 50 times the recommended max daily human intake. (31 Refs)

154. COMPARISON OF STUDIES ON SACCHARIN AND SODIUM NITRITE.

Taylor JM, Morgenroth VH
Div. Toxicology, Food and Drug Admin., Washington, DC, 20204
J Assoc Off Anal Chem; 62(4):883-888 1979

A review of long-term animal studies of saccharin and sodium nitrite was undertaken to assess the effect of variations in selected elements of protocol on the results obtained. These elements were divided into four general categories: design, including selection of test animals, basal diet, dosage form and doses of test substance, route of administration, and duration of exposure; observations, including gross observations during life and at necropsy, clinical tests, and histopathology; performance, including conduct of the test and animal husbandry; and analytical procedures, including chemical and statistical methods. Because many of these elements were not fully discussed in the study reports, it was often impossible to determine what actually had been done. The review of various saccharin studies suggested that bladder tumors resulted following in utero exposure, whereas in utero exposure to sodium nitrite did not appear to cause reticuloendothelial changes. The numerous variations in protocol in the nitrite studies precluded identification of a prime element responsible for the variations in reticuloendothelial changes observed. It can be concluded that achievement of reproducibility in long-term studies requires minimal variations in protocol for new studies. (11 Refs)

155. EXPERIMENTS ON THE CARCINOGENIC EFFECT OF ORTHO-TOLUOL-SULFONAMIDE (OTS).

Schmahl D
Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
Z Krebsforsch; 91(1):19-22 1978

The carcinogenicity of O-toluenesulfonamide (OTS), an essential impurity in saccharin prepared by the Remsen-Fahlberg method, was investigated in Sprague-Dawley rats. The OTS was mixed with the food and fed to the rats at daily doses doses of 200 and 20 mg/kg; the diets were continued for life. The max dose given amounted to 17 g/kg. No life-shortening effects were observed, and the incidence of malignant tumors in the OTS-treated animals was identical to that in a control group. However, one animal on the high-dose diet developed a urinary bladder carcinoma; four benign tumors were noted in four other animals in this group. Three animals in the low-dose group developed bladder papillomas. Although these results do not prove that OTS is carcinogenic, it is suggested that saccharin used in future experiments be kept as pure as possible. (8 Refs)

156. FEEDING STUDIES ON SODIUM CYCLAMATE, SACCHARIN AND SUCROSE FOR CARCINOGENIC AND TUMOUR-PROMOTING ACTIVITY.

Roe FJ, Levy LS, Carter RL
Chester Beatty Res. Inst. Cancer Res., London
Food Cosmet Toxicol; 8(2):135-145 1970

Female Swiss mice were fed a standard diet containing sucrose (10%), sodium cyclamate (5%) or saccharin (5%) for 18 mo following pretreatment with polyethylene glycol (PEG; 0.2 ml, by gastric intubation) or 3,4-benzpyrene (BP; 50 microg, in PEG). Although BP increased the frequency of tumors of the forestomach epithelium, further increases due to the sweetening agents, as cocarcinogens, were not observed. None of the sweeteners induced G.I. tumors or affect the occurrence of tumors of other organs, when admin alone. No urinary bladder tumors were detected by macroscopic examination in any of the mice. It is concluded that the sweetening agents had no carcinogenic or cocarcinogenic activity under these experimental conditions.

157. BLADDER TUMORS IN RATS FED CYCLOHEXYLAMINE OR HIGH DOSES OF A MIXTURE OF CYCLAMATE AND SACCHARIN.

Price JM, Biava CG, Oser BL, Vogin EE, Steinfeld J, Ley HL
5 references
Science; 167(3921):1131-1132 1970

This paper reviews the information presented to the National Academy of Sciences-National Research Council which led to the order that cyclamates be removed from the list of substances generally recognized as safe. In one study, a mixture of sodium cyclamate and sodium saccharin (10:1) was fed to Wistar rats (0-2500 mg/kg/day) over a period of about 2 yr. At the 79th week, half the rats were given cyclohexylamine hydrochloride (CHA) equivalent to conversion of 10% of their cyclamate dosage. Papillary tumors of the urinary bladder developed in 8/240 (7 males, 1 female-all receiving 2500 mg/kg). Three of the animals with tumors had received CHA. In another study, male and female Charles River-strain albino rats were given 0-15.0 mg of cyclohexylamine sulfate /kg/day. After 2 yr, one male rat of the 17 remaining alive in the high-dose group had a transitional-cell carcinoma of the urinary bladder.

158. LACK OF CARCINOGENIC ACTION FOR CYCLAMATE, CYCLOHEXYLAMINE AND SACCHARIN IN RATS.

Schmahl D
German Cancer Res. Inst., Heidelberg
Arzneim Forsch; 23(10):1466-1470 1973

An attempt was made to confirm the results of American investigators who found that artificial sweeteners produced bladder cancer in experimental animals. Seven groups of Sprague-Dawley rats, each consisting of 52 males and 52 females, were fed cyclamate (total doses of 882 or 2188 g/kg); saccharin (totals of 83 or 210 g/kg); cyclamate (totals of 750 or 1852 g/kg) + saccharin (totals of 75 or 185 g/kg); or cyclohexylamine (total of 177 g/kg). An untreated group of rats served as controls. The strain of rats employed had a high incidence of spontaneous tumors and developed bladder cancer after administration of butylbutanol nitrosamine. All rats were followed for their entire life span. Only one rat treated with 2% cyclamate developed a solitary bladder papilloma after 798 days. The bladder mucosa was normal in more than 95% of the rats. Parasites were present in the bladders of 16% of all cases and 8 older rats had bladder stones. None of the sweeteners tested had any effect on weight gain, blood picture, systolic blood pressure, morphology of the heart or bladder, survival time, or the incidence of any type of tumor. Despite its catecholamine-like action, cyclohexylamine had no effect on blood pressure and caused no morphological damage to the cardiovascular system.

159. LONG TERM TOXICITY AND REPRODUCTION STUDY (INCLUDING A TERATOGENICITY STUDY) WITH CYCLAMATE, SACCHARIN AND CYCLOHEXYLAMINE.

Kroes R, Kroes R, Peters PW, Berkvens JM, Verschuuren HG, De Vries T, Van Esch GJ
National Institute Public Health, P.O. Box 1, Bilthoven, Netherlands
Toxicology; 8(3):285-300 1977

Long-term studies of the toxicity, carcinogenicity, embryotoxicity, and teratogenicity of sodium cyclamate, saccharin, and cyclohexylamine in six generations of Swiss SPF outbred mice are reported. Each study included eight experimental groups: control, 5% or 2% sodium cyclamate, 10:1 mixture of 5% sodium cyclamate and 0.5% saccharin, 10:1 mixture of 2% sodium cyclamate and 0.2% saccharin, 0.5% or 0.2% saccharin, and 0.5% cyclohexylamine. Growth retardation, embryotoxicity, a tendency toward delayed ossification, and decrease in the number of implantations were noted in the cyclohexylamine groups. However, the survival of these animals was better than that of the controls and other treated groups. Tumor incidence was not increased in any group. A total of 7 bladder tumors and 34 cases of bladder calculi were noted in 2,400 animals. It was concluded that neither sodium cyclamate nor saccharin had toxic, embryotoxic or teratogenic effects and that none of the compounds were carcinogenic. (30 Refs)

160. TOXIC RESPONSE OF RATS TO CYCLAMATES IN CHOW AND SEMISYNTHETIC DIETS.

Friedman L, Richardson HL, Richardson ME, Lethco EJ, Wallace WC, Sauro FM
Bureau Foods, Food Drug Admin., Washington, D.C.
J Natl Cancer Inst; 49:751-764 1972

Cyclamates were fed to rats in two independently conducted studies. In study one, sodium and calcium cyclamate in commercial chow diets were fed, at dietary levels from 0.4-10%, to male and female weanling Osborne-Mendel rats for 101 weeks; in study two, 1 and 2% calcium cyclamate in semisynthetic diets containing 10 and 20% casein were fed to male weanling Holtzman rats for 75 weeks. In both studies, adverse reactions were noted. With the semisynthetic diet, growth rate was depressed, soft stools were produced, and the rate of kidney and urinary bladder lesions was increased. These adverse reactions did not appear to be affected by the protein content of the diet. No observed cytogenetic damage was produced by calcium cyclamate ingestion. With the chow diet, survival decreased and urinary bladder and kidney lesions increased; this increase was much more marked in severity and incidence than that with the semisynthetic diets. The lesions noted with the highest frequency in the kidneys were nephrocalcinosis and caliceal polyposis, and in the urinary bladder, epithelial hyperplasia, thickening or edema of the urinary bladder wall, and mucosal papilloma. Transitional cell carcinoma with varying degrees of invasion was detected in the urinary bladders of three of the 23 rats receiving calcium cyclamate in the chow diets. Two of these carcinomas were in rats fed diets containing only 0.4% of this compound. Bladder calculi were also occasionally present and were in two of the bladders with carcinomas. These lesions were not seen in any rats fed control diets.

161. BIOLOGICAL EFFECT AND HYGIENIC EVALUATION OF CYCLAMATES.

Pinter I, Czuczy P
Natl. Inst. Food Nutrition, Budapest, Hungary
Elelmiszervizsgalati Kozl; 19(1-2):29-34 1973

Studies on the acute and chronic toxicity as well as on the carcinogenic effect of cyclamates, first licensed for use as sweeteners in the USA in 1950, are reviewed. Chromosome breaks due to cyclamates and their metabolite, cyclohexylamine, were found in rat and in human lymphocytes, skin fibroblasts, and laryngeal cancer cells. The first indication of a possible carcinogenic effect of cyclamates was found in 1969 when mice developed cancer of the bladder in 16 months following placement of cholesterin balls containing 20% cyclamates in their bladders. Eight out of 80 rats having been fed 10:1 ratio of 2,500 mg of cyclamate/kg with saccharin developed cancer of the bladder. Cancer was not detected in a control group or in other rats fed 500 or 1,000 mg of cyclamate/kg. A slight, but distinct carcinogenic effect of cyclamates was detected in susceptible strains of mice that were fed 800 to 1,250 mg of cyclamate/kg during their lifetime starting from the 30th day of life. An epidemiological survey conducted in the USA in 1967 with the aim of establishing a possible relationship between the occurrence of cancer of the bladder in the population and cyclamate consumption was premature since the latency time of cancer in the human organism amounts to some 20 yr. In view of the rather scarce evidence of the carcinogenic effect of cyclamates, its use has been prohibited in the USA, and limited in Hungary.

162. LONG-TERM AND MULTIGENERATION TOXICITY STUDIES WITH CYCLOHEXYLAMINE HYDROCHLORIDE.

Oser BL, Carson S, Cox GE, Vogin EE, Sternberg SS
108-18 Queens Blvd., Forest Hills, NY 11375
Toxicology; 6(1):47-65 1976

To determine the toxicity of cyclohexylamine, a metabolite of cyclamate, and whether it is a causative or contributory agent in the induction of bladder tumors, cyclohexylamine hydrochloride was fed to FDRL weanling rats (15, 50, 100, and 150 mg/kg/day). Growth, feed efficiency, clinical and hematological tests, reproduction, teratology, mortality, and gross and microscopic pathology were studied. Rats from the first litters of each generation from F0 to F4 were studied. The physical and clinical observations were normal except for some non-progressive growth retardation in the higher dosage groups, due to lower food consumption. Reproduction rates were normal except in the higher dose groups which had smaller litters and lower weaning wt. At the 150 mg/kg level, there was mucosal thickening of the bladder walls and some renal calcification. No bladder tumors were seen as had been seen in a previous study in which rats were fed 2,500 mg/kg of a cyclamate:saccharin (10:1) mixture. There was a significantly higher incidence of testicular atrophy, characteristic of aged rats in the higher dose F0 group. These males continued to be fertile. (12 Refs)

163. LONG-TERM TOXICITY OF CYCLOHEXYLAMINE HYDROCHLORIDE IN MICE.

Hardy J, Gaunt IF, Hooson J, Hendy RJ, Butterworth KR
10, Heol Dowlais, Efail Isaf, Pontypridd CF38 1BB, Wales
Food Cosmet Toxicol; 14(4):269-276 1976

The effects of cyclohexylamine hydrochloride (CHAH), given over prolonged periods to ASH-CS1 mice, were evaluated. A total of 48 male and 50 female mice were divided into groups fed diets containing 0, 300, 1,000, or 3,000 ppm CHAH for 80 wk. No reductions were detected in the food intake of any CHAH-treated group compared with controls. The stomach wt of all three groups of female mice given CHAH were significantly lower than those of the controls. Most of the histopathological findings were similar in treated and control mice. Lesions found with a higher incidence in the treated animals were mild hepatic changes in the females given the highest dietary level, foamy hepatocytes in males at the intermediate level, and glomerulonephrosis in females at the lowest level. Tumors were found in all groups, but there were no significant differences between treated and control mice in

the incidences of the individual tumor types. Thus, CHAH exerts no carcinogenic effect at dietary levels up to 3,000 ppm; the non-untoward-effect level is 1,000 ppm. (18 refs)

164. LONG-TERM TOXICITY OF CYCLOHEXYLAMINE HYDROCHLORIDE IN THE RAT.
Gaunt IF, Hardy J, Grasso P, Gangolli SD, Butterworth KR
British Industrial Biological Res. Assoc., Woodmansterne Road, Carshalton, Surrey SM5 4DS, England
Food Cosmet Toxicol; 14(4):255-267 1976

The results of a 2-yr study to investigate the toxicity and carcinogenic potential of cyclohexylamine hydrochloride (CHAH) in Wistar rats are presented. The rats were given a diet containing 0, 600, 2,000, or 6,000 ppm CHAH. The food intakes of both sexes given 6,000 ppm CHAH were reduced compared with the controls. During the first year of the study, the Hb concentrations of the females given 6,000 ppm CHAH were consistently reduced by 6%-8% compared with the controls, and at 31 and 52 wk this was accompanied by reduced values for the packed cell volume. Many of the lesions encountered in the histopathological examination were present with a markedly lower frequency in the rats given 2,000 or 6,000 ppm CHAH than in the controls. This was particularly noticeable in the incidences of myocardial fibrosis, mild hepatic changes, hyperplasia of the parathyroids, and glomerulonephrosis. Only three tumors were present in rats given 6,000 ppm CHAH without parallel findings in controls. These were basal-cell carcinoma of the skin, osteosarcoma of the skull, and glioma in the brain. It is concluded that CHAH at levels up to 6,000 ppm in the diet does not demonstrate any carcinogenic potential and that the no-untoward-effect level is 600 ppm. (32 refs)

165. CANCER OF THE URINARY BLADDER INDUCED IN MICE WITH METABOLITES OF AROMATIC AMINES AND TRYPTOPHAN.
Allen MJ, Boyland E, Dukes CE, Horning ES, Watson JG
Br J Cancer; 11:212-228 1957

166. A CHRONIC STUDY OF ARTIFICIAL SWEETENERS IN SYRIAN GOLDEN HAMSTERS.
Althoff J, Cardesa A, Pour P, Shubik P
Cancer Lett; 1:21-24 1975

167. LONG-TERM TOXICITY STUDY WITH ORTHOTOLUENESULFONAMIDE AND SACCHARIN.
Arnold DL, Charbonneau SM, Moodie CA, Munro IC
Toxicol Appl Pharmacol; 41(1):164 1977

168. CHRONIC TOXICITY, TERATOLOGY AND MUTAGENICITY STUDIES WITH CYCLOHEXYLAMINE IN RATS.
Bailey DE, Morgareidge K, Cox GE, Vogin EE, Oser BL
Toxicol Appl Pharmacol; 22:330-331 1972

169. EFFECTS ON THE INTESTINAL MUCOSA OF THE RAT BY PROLONGED ADMINISTRATION OF CALCIUM CYCLAMATE.
Bernier JJ, Bognel JC, Bognel C
Bull Acad Nat Med (Paris); 152:7-18 1968

170. LONG TERM TOXICITY OF SODIUM CYCLAMATE IN MICE.
Brantom PG, Gaunt IF, Grasso P
Food Cosmet Toxicol; 11:735-746 1973

171. LONG TERM ADMINISTRATION OF ARTIFICAL SWEETENERS TO THE RHESUS MONKEY (M. MULATTA).
Coulston F, McChesney EW, Golberg L
Food Cosmet Toxicol; 13:297-299 1975

172. CHRONIC STUDIES WITH SODIUM SACCHARIN AND SODIUM CYCLAMATE IN DOGS.
Fancher PE, Palazzolo RJ, Blockus L, Weinberg MS, Calandra JC
Toxicol Appl Pharmacol; 12:291 1968

173. A COMPARISON OF THE CHRONIC TOXICITIES OF SYNTHETIC SWEETENING AGENTS.
Fitzhugh OG, Nelson AA, Frawley JP
J Am Pharmacol Assoc; 40:583-586 1951

174. LONG-TERM TOXICITY STUDY OF SODIUM CYCLAMATE AND SACCHARIN SODIUM IN RATS.
Furuya T, Kawamata K, Kaneko T, Uchida O, Horiucho S, Ikeda Y
Jpn J Pharmacol; 25:55P-56P 1975

175. NEGATIVE LIFETIME CARCINOGEN STUDIES IN RATS AND MICE FED 50,000 PPM SACCHARIN.
Homburger F
Chemical Toxicology of Food, Development in Toxicology and Environmental Science. Galli CL, Paoletti R, Vettorazzi G, ed. Elsevier, North Holland, Vol. 3, 1978.

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177. EFFECT OF FEEDING CALCIUM CYCLAMATE TO RATS.
Nees PO, Derse PH
Nature (Lond); 211:1191-1195 1967

178. CHRONIC TOXICITY STUDY OF CYCLAMATE: SACCHARIN (10:1) IN RATS.
Oser BL, Carson S, Cox GE, Vogin EE, Sternbery SS
Toxicology; 4:315-330 1975

179. URINARY BLADDER CARCINOMA AND OTHER PATHOLOGICAL ALTERATIONS IN RATS FED CYCLAMATES.
Richardson HL, Richardson ME, Stewart HL, Lethco EJ, Wallace WC
Proc Am Assoc Cancer Res Am Soc Clin Oncol; 13:2 1972

180. STUDIES ON THE CARCINOGENIC EFFECT OF SODIUM CYCLAMATE IN MICE.
Rudali G, Coezy E, Muranyi Kovacs I
Comptes Rendus Hebdomadaires Seances Acad Sci; 269:1910-1912 1969

181. FURTHER TESTS FOR TUMOR INITIATING ACTIVITY: N,NDI-(2-CHLOROETHYL)-P-AMINOPHENYLBUTYRIC ACID (CB1348) AS AN INITIATOR OF SKIN TUMOR FORMATION IN THE MOUSE.
Salaman MH, Roe FJC
Br J Cancer; 10:363-378 1956

182. LONG TERM STUDIES ON THE POTENTIAL CARCINOGENICITY OF ARTIFICIAL SWEETENERS IN NON-HUMAN PRIMATES.
Sieber SM, Adamson RH
Proceedings of Conference on Health and Sugar Substitutes, Basel, Karger. pp. 266-271, 1978.

183. HYPERACTIVITY IN RATS BRED AND RAISED ON RELATIVELY LOW AMOUNTS OF CYCLAMATES.
Stone D, Mataika E, Riordan J
Nature (Lond); 224:1326-1328 1969

184. TOXICOLOGICAL STUDIES WITH SODIUM CYCLAMATE AND SACCHARIN.
Taylor JD, Richards RK, Wiegand RG, Weinberg MS
Food Cosmet Toxicol; 6:137-142 1968

185. LONG TERM FEEDING OF SACCHARIN TO RATS.
Tisdel MO, Nees PO, Harris DL, Derse PH
Symposium: Sweeteners. Inglett GE, ed. Avi. Publishing Company, Westport, Connecticut, pp. 145-158, 1974.

186. A TOXICITY METHOD WITH CALCIUM CYCLAMATE FOR CHRONIC CARCINOGENESIS.
Toth B
Tumori; 58:137-142 1972

187. CHRONIC TOXICITY AND CARCINOGENICITY OF INDUSTRIAL CHEMICALS AND PESTICIDES.
Ulland B, Weisburger EK, Weisburger JH
Toxicol Appl Pharmacol; 25:446 1973

188. TOXIC RESPONSE OF RATS TO CYCLAMATES IN CHOW AND SEMISYNTHETIC DIETS.
Wallace WC, Sauro FM, Friedman L, Richardson HL, Richardson ME, Lethco EJ
J Natl Cancer Inst; 49:751-764 1972

V. ARTIFICIAL SWEETENERS AS TUMOR PROMOTERS OR COCARCINOGENS

189. SACCHARIN: FROM CARCINOGEN TO PROMOTER.
Boyland E
London Sch. Hygiene and Tropical Medicine, London, England
Nature (Lond); 278(5700):123-124 1979

Evidence that saccharin may be a promoting agent rather than a complete carcinogen is reviewed. In eight studies in which saccharin was fed to rats, the bladder tumor incidence was never more than 44% and was usually lower, even when the diets contained 5% saccharin. When small initiating doses of methyl nitrosourea were instilled into the urinary bladder of Wistar rats, no bladder tumors were detected. Of the rats that were subsequently given saccharin in drinking water, 57% developed tumors. Similar results were obtained when rats were fed 2% N-(4-(5-nitro-2-furyl)-2-thiazolyl)formamide (FANF) followed by 5% saccharin. Cultures of C3H/10T1/2 cells treated with nontransforming initiating doses of methylcholanthrene + saccharin had a statistically significant number of transformations. These experiments indicate that saccharin is a promoter rather than a direct carcinogen. Although saccharin may not be harmless, it is unlikely to be a serious hazard because the dose required to produce the promoting effect is so large (1 kg/kg body wt). (18 Refs)

190. CO-CARCINOGENIC ACTION OF SACCHARIN IN THE CHEMICAL INDUCTION OF BLADDER CANCER.
Hicks RM, Wakefield JS, Chowaniec J
Middlesex Hosp. Med. Sch., London, England
Nature (Lond); 243(5406):347-349 1973

The effect of dietary saccharin (2 g/kg body wt/day) on the development of bladder carcinoma was studied in female Wistar rats which received a single intravesicular instillation of N-methyl-N-nitrosourea (NMU). Whereas controls which received NMU alone showed a transient hyperplastic response of the bladder epithelium, 9 of 12 animals receiving both NMU and saccharin developed gross hyperplasia with capillary invasion (4 animals), papillary or nodular outgrowths (2 animals), or frank invasive carcinoma (3 animals). Controls fed saccharin alone showed slowly developing, mild bladder hyperplasia over the same time period.

191. HISTOLOGY OF TUMOUR FORMATION IN THE BLADDER OF RATS RECEIVING DIETARY SACCHARIN AND A SINGLE DOSE OF N-METHYL N-NITROSOUREA (MEETING ABSTRACT).
Chowaniec J, Hicks RM, Wakefield JS
Middlesex Hosp. Medical Sch., London, England
Br J Cancer; 29(1):93 1974

Previous studies have indicated that dietary saccharine can act as a cocarcinogen with N-methyl N-nitrosourea at doses at which neither alone produces tumors. The incidence of further bladder tumors in animals from this and other experiments using higher doses of saccharin confirmed this observation. Most tumors were epithelial, and varied from papillary outgrowths and sessile transitional cell tumors to invasive squamous metaplasia. Some sarcomata were also observed. The rise in urinary pH in animals receiving saccharin predisposed to the formation of urinary calculi in the bladder, ureters and kidney. Histological examination indicated that some calculi originated below the epithelium. This suggests a breakdown of the normal epithelial permeability barrier, thus allowing the pH of the tissue fluids in the bladder wall to rise in parallel with the urine.

192. PROMOTING EFFECT OF DL-TRYPTOPHAN AND SACCHARIN IN URINARY BLADDER CARCINOGENESIS IN THE RAT (MEETING ABSTRACT).
Cohen SM, Arai M, Friedell GH
Dept. Pathology, St. Vincent Hosp., Worcester, MA, 01604
Proc Am Assoc Cancer Res; 19:4 1978

The effect of feeding DL-tryptophan (2% of diet) or saccharin (5%) to male weanling Fischer rats alone or after 6 wk of 0.2% N4-(5-nitro-2-furyl)-2-thiazolylformamide (FANFT) was evaluated over a 2-yr experimental period. Bladder papilloma developed in none and carcinoma in 3/19 rats fed 6 wk of FANFT followed by control diet, and 20/20 rats fed FANFT for 36 wk followed by control diet developed carcinoma. FANFT for 6 wk followed immediately by DL-tryptophan resulted in papilloma in 1 and carcinoma in 9/19 rats, whereas papilloma developed in 7 and carcinoma in 7/20 rats fed DL-tryptophan after 6 wk of FANFT and 6 wk of control diet. Saccharin after 6 wk of FANFT induced papilloma in 1 and carcinoma in 17/19 rats, and saccharin fed after 6 wk of FANFT plus 6 wk of control diet resulted in papilloma in 4 and carcinoma in 9/18 rats. Most of the rats fed tryptophan survived to the end of the experiment (104 wk), whereas rats administered saccharin after FANFT, or after FANFT and control diet, had decreased survival usually due to hematuria secondary to tumor formation with av survival of 93 and 96 wk, respectively. No bladder tumors were observed in 18 rats administered only tryptophan, 20 rats fed saccharin, or 40 rats fed control diet only. Mild bladder hyperplasia was observed in rats at the end of the 6th wk of FANFT, but regressed to normal after 6 wk of control diet. DL-tryptophan and saccharin enhanced bladder carcinogenesis when administered immediately after 6 wk of FANFT or after 6 wk of FANFT plus 6 wk of control diet.

193. PROMOTING EFFECT OF SACCHARIN AND DL-TRYPTOPHAN IN URINARY BLADDER CARCINOGENESIS.
Cohen SM, Arai M, Jacobs JB, Friedell GH
Dept. Pathology, St. Vincent Hosp., Worcester, MA, 01604
Cancer Res; 39(4):1207-1217 1979

The existence of at least two stages in bladder carcinogenesis was investigated in male Fischer rats using N4-(5-nitro-2-furyl)-2-thiazolylformamide (FANFT: 0.2% of diet

for 6 wk; av cumulative dose 1.5 g) as the initiator. Sodium saccharin (SS) and DL-tryptophan (TP) were fed at 5% and 0.2% of the diet, respectively, starting either immediately after or 6 wk after FANFT administration. After 2 yr, rats fed the control diet (42 rats), SS (20), or TP (20) had no urinary bladder lesions. The group fed FANFT followed by control diet developed one papilloma and four bladder carcinomas. All rats fed FANFT for 36 wk or for their lifetime (78 rats) had bladder carcinomas, and several had invasive lesions. Rats fed FANFT + SS or TP, either immediately after FANFT feeding or after FANFT + 6 wk of control diet, developed high incidences of bladder cancer. SS was a much more potent promoting agent than TP, inducing higher incidences of bladder tumors with a shorter latent period and producing tumors that were more invasive. Sequential epithelial changes were observed by scanning and transmission electron microscopy as well as by light microscopy. Pleomorphic microvilli were present on the superficial cells of all tumors examined and on the surface cells of hyperplastic bladder epithelium after 6 wk of FANFT + 6 wk of SS, but not after 6 wk of FANFT + 6 wk of control diet or 6 wk of TP. These results are consistent with the two stage theory of urinary bladder carcinogenesis and suggest that SS and TP might act as tumor-promoting agents. (68 Refs)

194. NUTRITIONAL FACTORS THAT MAY BE INVOLVED IN CANCER OF THE BLADDER.

Friedell GH, Greenfield RE, Cohen SM
St. Vincent Hosp., 25 Winthrop St., Worcester, MA, 01604
Nutr Cancer; 1(2):82-88 1979

Studies of the relationship between nutrition and bladder cancer (BlC) are reviewed. Elevated amounts of kynurenine, hydroxykynurenine, acetylkynurenine, and kynurenic acid were excreted by 50% of a group of BlC patients who had no history of occupational exposure to aromatic amines. However, BlC patients with known exposure to industrial amines did not exhibit abnormal tryptophan (TP) metabolite excretion patterns. In another study, 17% of BlC patients from an urban area had abnormal TP metabolite excretion patterns, compared with 47% of a group of patients from an agricultural area. These results suggest that TP metabolites may have a role in the etiology of so-called spontaneous BlC, but probably have little to do with the development of industrial or environmental BlC. In Fischer rats fed the carcinogens N4-(5-nitro-2-furyl)-2-thiazolylformamide (FANFT) or N-methyl-N-nitrosourea (MNU), both saccharin and sodium cyclamate acted as BlC promoters. In similar studies, TP also acted as a promoting agent. Pyridoxine (vitamin B6: 25 mg/day) restores an abnormal pattern of excretion of urinary TP metabolites to a normal pattern and also apparently diminishes the frequency of recurring BlC. Vitamin A and vitamin C also appear to have some beneficial effects in inhibiting the induction of BlC in experimental animals. (29 Refs)

195. ENHANCEMENT OF ONCOGENESIS IN C3H/10T1/2 MOUSE EMBRYO CELL CULTURES BY SACCHARIN.

Mondal S, Brankow DW, Heidelberger C
Comprehensive Cancer Center, Univ. Southern California, Los Angeles, CA, 90033
Science; 201(4361):1141-1142 1978

The transforming and promoting activities of saccharin were studied in vitro using C3H/10T1/2, clone 8, mouse embryo fibroblasts. At 2 mg/ml, saccharin alone was nontoxic and nontransforming, and it had no initiating effect when followed 4 days later by continuous treatment with 12-O-tetradecanoylphorbol-13-acetate (TPA). However, both pure and impure samples of saccharin (100 ug/ml) showed significant cocarcinogenic activity during continuous treatment of cultures initiated with 3-methylcholanthrene (0.1 ug/ml). TPA, but not saccharin, promoted UV-initiated cells. The reason for this difference between these otherwise equivalent initiators is not clear. Nevertheless, the results suggest that saccharin acts as a promoter and that caution should be applied to the indiscriminate or long-term use of saccharin in human nutrition. (22 Refs)

196. INDUCTION OF INCREASED FREQUENCIES OF SISTER CHROMATID EXCHANGE IN V79 CELLS BY BUTYRIC ACID (MEETING ABSTRACT).

Tai CC, Ting RC
Biotech Res. Lab., Incorporated, Rockville, MD, 20852
In Vitro; 15(3):172 1979

Butyric acid has been shown to induce reversible inhibition of cell proliferation and morphological differentiation in several cultured cell lines. In the present study, similar effects were observed in V79 cells in the presence of this compound. Other short-chain fatty acids, propionic, valeric as well as crotonic, were also found to affect cell growth but without affecting cell morphology at higher concentrations. By applying 5'-bromodeoxyuridine (BUdR) and differential staining techniques, it was found that sodium butyrate elevated the frequencies of sister chromatid exchange (SCE) in these cells. At 5.0 milliM, a 3-4 fold increase in SCE was observed. At comparable concentration the other short-chain fatty acids only induced slight increases in SCE in V79 cells. A synergistic effect on SCE was observed when both butyrate and saccharin were present simultaneously in the culture medium. Caffeine did not significantly affect SCE, either alone or in conjunction with butyrate, saccharin or both. Chromosomal aberrations were not produced in these cells when grown with these compounds. The possible mechanism involved in the induction of SCE by butyric acid is discussed in light of the repression of excision repair under differentiated state of a cell. (no Refs)

197. THE IMPORTANCE OF SYNERGY BETWEEN WEAK CARCINOGENS IN THE INDUCTION OF BLADDER CANCER IN EXPERIMENTAL AMINALS AND HUMANS.

Hicks RM, Chowaniec J
Sch. Pahtology, Middlesex Hosp. Medical Sch., London, W1P 7LD, England
Cancer Res; 37(8,part2):2943-2949 1977

It is now well established that the interaction of multiple environmental factors may increase the incidence of some human cancers more than exposure to a single carcinogen. With an in vivo experimental rat model, we have demonstrated a synergistic effect in bladder carcinogenesis between a subcarcinogenic dose of the strong bladder carcinogen, N-methyl-N-nitrosourea, and saccharin- or cyclamate-containing diets. If these artificial sweeteners are capable of interacting with other environmental bladder carcinogens, their potential for increasing the incidence of human bladder cancer is greater than many more potent chemical carcinogens, because of their wide distribution as food additives to all sections of the population. Retrospective epidemiology shows no evidence of such risk from saccharin at current levels of consumption. No comparable studies are available for cyclamate, which was consumed in greater quantities but for relatively few yr. It is emphasized that it is possible for interaction between multiple factors to contribute to the incidence of human bladder cancer as it does in other human organs and in other animal species. (Author abstract) (43 Refs)

198. EVALUATION OF A NEW MODEL TO DETECT BLADDER CARCINOGENS OR CO-CARCINOGENS; RESULTS OBTAINED WITH SACCHARIN, CYCLAMATE AND CYCLOPHOSPHAMIDE.

Hicks RM, Wakefield JS, Chowaniec J
Middlesex Hosp. Medical Sch., London, W1P 7LD, Great Britain

Chem Biol Interact; 11(3):225-233 1975

A sensitive model was designed to detect potential weak bladder carcinogens or cocarcinogens. The test compound is given to Wistar rats which have received a single intravesicular initiating but noncarcinogenic, dose of N-methyl-N-nitrosourea (MNU, 2.0 mg). The model was used to investigate two compounds currently under suspicion as weak bladder carcinogens, sodium saccharin and sodium cyclamate ; and one compound known to be cytotoxic but not carcinogenic for the bladder epithelium, cyclophosphamide . The three compounds were also tested as solitary carcinogens in animals not pretreated with MNU. At very high dose levels, sodium saccharin (2.0 or 4.0 g/kg/day for life) and sodium cyclamate (1.0 or 2.0 g/kg/day for life) were weak solitary carcinogens producing four bladder tumors in 253 mice and three in 228, respectively. The first of these tumors did not appear for more than 80 wk. When tested in the MNU rat model, more than half the animals receiving either sodium saccharin or sodium cyclamate developed bladder tumors from ten weeks onward. By contrast, cyclophosphamide failed to produce any tumors when tested, either as a solitary carcinogen (18 monthly ip injections of 100 mg/kg) or in the MNU rat model (single ip injection of 200 mg/kg, given either two weeks before or two weeks after intravesicular dose of 2.0 mg MNU). The doses of saccharin and cyclamate used were far higher than those consumed by man, including diabetics, and these results should not be directly extrapolated to man without careful consideration of many other factors including negative epidemiological findings. The theoretical basis of the model is discussed, and also the relevance, in terms of environmental human exposure, of detecting compounds having a synergistic effect with other known bladder carcinogens. It appears that this model can be used to detect a carcinogenic or cocarcinogenic potential in compounds that are organotropic for the bladder more rapidly and with fewer animals than if the compounds are tested as solitary carcinogens by more conventional methods.

199. INHIBITORY EFFECT OF SODIUM CYCLAMATE AND SODIUM SACCHARIN ON TUMOR INDUCTION BY 2-ACETYLAMINOFLUORENE IN RATS (MEETING ABSTRACT).

Ershoff BH, Bajwa GS
Inst. Nutritional Studies, Culver City, Ca.

Proc Soc Exp Biol Med; 145(4):1293-1297 1974

The effects of orally administered sodium cyclamate and sodium saccharin on tumor incidence was studied in 48 female Horton-Sprague-Dawley rats fed the carcinogen 2-acetylaminoflorene (AAF). Of 12 rats fed a natural food stock ration supplemented with 300 mg AAF/kg diet, 11 (91.7%) developed palpable mammary and ear duct tumors during a 40-week period in contrast to a tumor incidence of 2 out of 12 rats (16.7%) fed a similar ration supplemented with 5% sodium cyclamate and 6 of 12 rats (50%) fed a diet containing 5% sodium saccharin. Judging by gross and microscopic examination of the livers of surviving rats after the 40 week period, administration of sodium cyclamate and sodium saccharin also resulted in a marked reduction in the size of liver tumors of rats fed AAF. The mechanism by which sodium cyclamate and sodium saccharin produce these protective effects is not known at the moment.

200. INDUCTION OF DIFFERENTIATION IN HUMAN PROMYELOCYTIC LEUKEMIA CELLS BY TUMOR PROMOTERS.

Rovera G, O'Brien TG, Diamond L
Wistar Inst. Anatomy and Biology, Philadelphia, PA, 19104

Science; 204(4395):868-870 1979

The ability of some tumor promoters to induce differentiation was studied in HL-60 cells derived from the peripheral blood WBC of a woman with acute promyelocytic leukemia. Phorbol diester tumor promoters and the promoter mezerein converted cultured HL-60 cells into adherent, nonproliferating cells with many of the characteristics of macrophages; the conversion was very rapid and affected 100% of the HL-60 population. Other types of promoters, including anthralin, phenobarbital, and saccharin, did not have this effect. A major determinant of the cell response to the promoters appeared to be the target cell, ie, whether it was a unipotent or multipotent stem cell. The chemical structure of the promoter was also important in that only diterpene esters that are promoters in vivo induced adherence and differentiation in HL-60 cells. The results suggest that mezerein and similar compounds merit further investigation as antitumor drugs that may be able to force leukemia cells to differentiate into nonproliferating macrophagelike cells. (23 Refs)

201. LACK OF CYCLAMATE SYNCARCINOGENICITY IN BUTANOL-BUTYL-NITROSAMINE-INDUCED URINARY BLADDER CARCINOGENESIS IN RATS.

Schmahl D, Kruger FW
German Cancer Res. Ctr., Heidelberg, W. Germany

Arzneim Forsch; 22(6):999-1000 1972

One hundred and twenty 100 day-old male Sprague-Dawley rats were distributed into three groups to test the syncarcinogenicity of cyclamate in 4-hydroxybutanol-b butylnitrosamine (BBN)-induced carcinogenesis. One group received 10 mg/kg/day of BBN in their drinking water, the other group received 2,500 mg/kg/day of cyclamate in their diet, in addition to a similar dose of BBN; the third group received no treatment. The feeding experiment lasted 400 days. All 40 rats receiving BBN alone died of squamous cell carcinoma of the bladder which developed after an average latency period of 400 plus or minus 45 days. Twenty seven of the 40 rats which underwent combined treatment had typical urinary bladder carcinomas, and 2 had extensive bladder papillomatosis; 20 of these rats died 440 days after the beginning of the experiment. The surviving 11 rats exhibited hematuria and were suspect of bladder carcinoma. Regression curves for the two groups, plotted with the tumor incidence as ordinate and the latency period as abscissa, were parallel. The high dose of cyclamate produced no enhancement of BBN-induced carcinogenesis. No urinary bladder alterations occurred in the control group.

202. STUDIES ON THE CORRELATION BETWEEN THE CHANGE IN DELTA-4-STEROID HYDROGENASE ACTIVITY AND THE DEVELOPMENT OF LUNG TUMOR IN RATS AFTER THE ADMINISTRATION OF BENZPYRENE.

Ichiyoshi T
Dept. Medicine, Kasumigaura Branch-Hosp., Tokyo Medical and Dental Univ., Inashiki-gun, Ibaragi Pref., 300-03, Japan

Lung Cancer (Haigan); 17(1):11-19 1977

For the purpose of clarifying the mechanism of altered metabolism of steroid hormones in tumor-bearing animals, delta-4-steroid hydrogenase activity in the livers of female strain SD rats, which were treated with intratracheal administration of benzpyrene, was examined for 9 mo. Rats

were divided into four groups: normal group, benzpyrene group (intratracheal infusion of 10 mg), benzpyrene and prednisolone group (0.25 mg per 100 ml of drinking water ad libitum), and benzpyrene and xylitol group (1% xylitol in drinking water ad libitum). Delta-4-steroid hydrogenase activity was determined using H3-corticosterone as substrate. Delta-4-steroid hydrogenase activity in the livers of malignant lung tumor developing rats was significantly decreased. In benzpyrene treated but non-tumor bearing rats, the enzyme activity remained at its normal level. In the group which was treated with additional use of prednisolone, development of the histologically malignant lung tumors was accelerated. It was suggested that by the combined use of xylitol after the administration of carcinogenic substance, the development of malignant tumor was delayed. Throughout the experiments, the existence of delta-4-steroid-hydrogenase-suppressing factors in tumor-developing rats was suggested, and it was also suggested that a high level of plasma glucocorticoids might accelerate the tumor incidence. (27 Refs)

203. ADVANCEMENT OF CANCER THROUGH NONCARCINOGENS (TUMOR PROMOTORS).

Judes BU
Am Teich 1, 2418 Giesensdorf, W. Germany
Naturwiss Rundsch; 32(8):322-323 1979

The synergistic effects of carcinogens and tumor promotors, such as phorbol esters, saccharin, sodium cyclamate, phenobarbital, bile acids, and promotors in cigarette smoke, are discussed and a two-step model of tumor development is presented. Different theories of the actions of carcinogens and tumor promotors are summarized. (6 Refs)

204. TUMOR PROMOTERS: CARCINOGENESIS GETS MORE COMPLICATED.

Marx JL
No affiliation given.
Science; 201(4355):515-518 1978

Promotion is important in the development of several cancers in a variety of species, and many carcinogens may have the ability to both initiate and promote tumor formation. The initiation step is irreversible, but if exposure to promoter is stopped before the cells gain the ability to multiply in the absence of the promoter, tumor formation may be avoided. Among the chemicals with promoting activity are the phorbol esters; phenobarbital, which appears to promote liver tumors; saccharin and sodium cyclamate, which appear to promote bladder tumors; bile acids, which promote the development of colon cancer; and cigarette smoke. Most investigators think that initiation involves an alteration in the cell's DNA by the initiating agent. Tumor promoters appear to interfere with the normal development of cells. All promoters tested increased cellular ornithine decarboxylase activity, which may be a prerequisite for promotion. Proteases are also implicated in this respect. It is possible that promoters bind to a receptor for a naturally occurring material, namely, epidermal growth factor (EGF), which stimulates the division of epidermal cells. There may be several stages in the progression of initiated cells to benign and then to malignant tumors. Since the effects of promotion are reversible, it may be possible to use inhibitors to prevent cancers from developing. (no Refs)

205. EXPERIMENTAL INDUCTION OF BLADDER TUMORS BY A TWO-STAGE SYSTEM.

Hicks RM, Chowaniec J, Wakefield JStJ
Carcinogenesis. Raven Press, New York, Vol. 2, pp. 475-489, 1978.

206. SYNCARCINOGENIC ACTION OF SACCHARIN AND SODIUM CYCLAMATE IN THE INDUCTION OF BLADDER TUMORS IN MNU-PRETREATED RATS.

Mohr U, Green U, Althoff J, Schneider P
Proceedings of the European Research Group for Oral Biology, Conference on Sugar Substitutes. Basel S, ed. Karger, in press, 1979.

VI. GENETIC TOXICITY STUDIES

A. Reproduction, Fertility and Teratogenicity Studies

207. MUTAGENICITY TESTS WITH CYCLOHEXYLAMINE IN THE MOUSE.

Cattanach BM, Tollard CE
M.R.C. Radioactivity Unit, Didcot, Berks., England
Mutat Res; 12:472-474 1971

Male F1 offspring of matings of C3H female mice with strain 101 male mice were given ip injections of cyclohexylamine totalling 250 or 500 mg/kg and mated with females; mated females were sacrificed at 14-16 days gestation and the proportion of pre- and post-implantation deaths caused by dominant lethal mutations induced by cyclohexylamine was ascertained. There was no indication that cyclohexylamine at the doses given induced significantly elevated frequencies of pre- or post-implantation deaths. In a related experiment, testis preparations from cyclohexylamine-treated and from untreated male mice were examined for chromosome translocations; 1 of the 8 untreated controls showed a translocation while none of the 12 mice given either 50 or 100 mg/kg cyclohexylamine showed translocations. The results suggested that cyclohexylamine, even at high dose levels, dose not induce heritable chromosome breakage either in the postmeiotic germ cells or in the spermatogonia of the mouse.

208. DOMINANT-LETHAL EFFECTS OF CYCLOHEXYLAMINE IN C57BI/FE MICE.

Petersen KW, Legator MS, Figge FH
Dept. Hlth., Educ. Welfare, Washington, D. C.
Mutat Res; 14(1):126-129 1971

Male C57 BI/Fe mice (20-25 g), 12 weeks of age, were divided into three groups of ten mice each. The mice of one group were given ip injections of cyclohexylamine (CHA) in saline (adjusted to pH 7.2 with 0.1 N HCl) at a dose of 100 mg/kg daily for five days. A saline solution of triethylenemelamine (TEM), the positive control compound, was administered to another group for five consecutive days at a dose of 0.05 mg/kg. Mice in the third group were given injections of 0.5 ml of saline. Immediately after the last injection, each male was caged separately with three female mice (C57 BI/Fe) for one week. Two additional weekly matings were made. Twelve days after the end of the last day of mating, the uterine contents were examined for viable implants, dead implants and late fetal deaths. The percentage of dead implants in the TEM-treated group showed the normal decline through the third week. With CHA treatment, the dead implants increased from 13.3% the first week to 15.6% the second week and to 18% the third week; dead implants from the saline treated control mice averaged 4.8% during the three weeks.

209. MUTAGENICITY STUDIES OF SACCHARIN IN MICE.

Sram RJ, Zudova Z
Inst. Hyg. Epidemiol., Prague, Czechoslovakia
Bull Environ Contam Toxicol; 12(2):186-192 1974

Studies were conducted on ICR male mice treated with single or repeated ip injections of saccharin to determine the mutagenicity and, hence, genetic risk of saccharin use. Following treatment, male mice were mated with female mice. The latter were autopsied between day 13-19 of pregnancy and scored for corpora lutea, total number of implants, early and late fetal deaths, and live embryos. Total dominant lethality was calculated from these data. None of the treatment regimens affected male fertility. Treatment with a single dose of 1000 mg/kg or with 5 divided doses of 200 mg or 100 mg/kg resulted in an increase in preimplantation lethality compared with controls. Total dominant lethality was increased in animals treated with 5 divided doses of 200 mg/kg every 24 hr, 100 mg/kg every 12 hr, or 200 mg/kg every 12 hr. The highest frequency of dominant lethals was found in the group receiving 5 x 200 mg/kg every 12 hr. In general, the incidence of dominant lethals increased with increasing dose levels. Cytologic analysis of chromosome rearrangements in spermatogonia showed that 5 x 200 mg/kg saccharin every 12 hr produced 1.6% translocations and 4.5% separated X and Y chromosomes (univalents).

210. PRELIMINARY STUDIES ON MUTAGENICITY OF SACCHARIN BY INDUCTION OF DOMINANT LETHALS.

Tezabwala BU, Gothoskar SV
ICMR Unit for Studies on Environmental Carcinogens, Cancer Res. Inst., Parel, Bombay-400 012, India
Indian J Cancer; 14(3):232-234 1977

Male C17 and Swiss mice were injected sc with 100, 240, or 480 mg/kg saccharin and then mated with females of the same strain. A significant number of dominant lethal mutations defined as the ratio of deciduo mate and dead embryos to the total number of embryos, were noted during the second and third wk in C17 mice whose mates had been treated with 240 or 480 mg/kg. In Swiss mice, the effect was only significant during the third wk of pregnancy in mice whose mates had received 240 mg/kg. (13 Refs)

211. EXPERIENCES WITH THE DOMINANT LETHAL TEST IN FEMALE MICE: EFFECTS OF ALKYLATING AGENTS AND ARTIFICIAL SWEETENERS ON PRE-OVULATORY OOCYTE STAGES.

Machemer L, Lorke D
Bayer AG, Institut fuer Toxikologie, Wuppertal-Elberfeld (W. Germany
Mutat Res; 29(2):209-214 1975

The study of dominant lethal effects in female mice was undertaken in an attempt to develop a procedure for screening potential mutagenic substances early in the product development stages. Female mice were considered to be especially useful for these purposes because (a) the preovulatory oocytes are especially sensitive to mutagenic influences, and (b) the post-dictyotenc oocytes, not being subject to selection and elimination before fertilization, may reveal mutagenic effects directly and unrestrictedly. In the procedure developed for screening purposes, vaginal smears were taken at about 3 p.m, and the estrus phases of the female mice were examined. Animals in pre-estrus received a single dose of the test compound, and at about 4 p.m were mated with untreated males. Females that had a vaginal plug the following morning were rated as inseminated and remained in the trial. Two weeks after the appearance of the vaginal plug the females were sacrificed and dissected and evaluated as in the usual dominant lethal test. The screening procedure was tested with artificial sweeteners and alkylating agents. The following treatments induced dominant lethal effects: methyl methanesulfonate , 100 mg/kg im; cyclophosphamide , 200 mg/kg po; and triaziquone , 0.25 mg/kg ip. The following agents were ineffective and may be classified as not mutagenic in this method: sodium cyclamate 10,000 mg/kg po; saccharine sodium , 10,000 mg/kg po; cyclohexamine sulfate 150 mg/kg po; and ethanol 5 ml/kg po. Several advantages are claimed for the proposed screening system; this includes the fact that if no lethal effect occurs, then absence of mutagenic action, and the absence of action on ovulation, fertilization, and cleavage can be deduced. If lethal effects are found, however, they do not prove mutagenic action; action on other processes of reproduction is also possible, and further studies using other test systems are necessary.

212. CHEMICAL INDUCTION OF SPERM ABNORMALITIES IN MICE (MEETING ABSTRACT).

Wyrobek AJ, Bruce WR
Ontario Cancer Institute, 500 Sherbourne Street, Toronto, Ontario M4x 1k9, Canada
Proc Natl Acad Sci USA; 72(11):4425-4429 1975

The sperm of (C57BL x C3H)F1 mice were examined 1, 4, and 10 weeks after a subacute treatment with one of 25 chemicals at two or more dose levels. The fraction of sperm that were abnormal in shape was elevated above control values of 1.2-3.4% for methyl methanesulfonate, ethyl methanesulfonate griseofulvin benzo(a)pyrene METEPA TRIS (2-methyl-1-aziridinyl)phosphine oxide , THIOTEPA TRIS (1-aziridinyl)phosphine sulfide mitomycin C myleran vinblastine sulphate hydroxyurea 3-methylcholanthrene colchicine actinomycin D imural cyclophosphamide 5-iododeoxyuridine dichlorvos aminopterin and trimethylphosphate Dimethylnitrosamine urethane DDT (1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane), 1, 1-dimethylhydrazine caffeine, and calcium cyclamate did not induce elevated levels of sperm abnormalities. The results suggest that sperm abnormalities might provide a rapid inexpensive mammalian screen for agents that lead to errors in the differentiation of spermatogenic stem cells in vivo and thus indicate agents which might prove to be mutagenic, teratogenic, or carcinogenic.

213. EVALUATION OF THE MUTAGENIC POTENTIAL OF CYCLOHEXYLAMINE ON SPERMATOGONIA OF THE CHINESE HAMSTER.

Machemer L, Lorke D
Institut fur Toxikologie, BAYER AG, Wuppertal-Elberfeld, West Germany
Mutat Res; 40(3):243-250 1976

Cyclohexylamine (neutral sulfate) was evaluated for its mutagenic effects on Chinese hamster spermatogonia in comparison with an untreated control group and a group treated with cyclophosphamide by assessing the spermatogonial metaphases of treated hamsters for chromosomal structural changes. Approx 100 metaphases from each animal were assessed. The doses were 5 x 150 mg cyclohexylamine sulfate/kg and 5 x 100 mg cyclophosphamide/kg po. The individual doses were administered at intervals of 24 hr. Preparations were made 24 hr after the final treatment. Gaps, breaks, fragments, deletions, and translocations were assessed as structural changes; frequencies were determined of the metaphases with aberrations, including gaps; with aberrations less gaps; and with translocations. Aberrations occurred in the untreated negative control group

(1.24%, including gaps; 0.25% without gaps). Translocations were not seen in the untreated group. In the cyclohexylamine group, the frequencies of the aberrant metaphases were sometimes less than in the control group (0.87%, including gaps; 0.37% without gaps). The results were not significantly different from the control data. No translocations occurred after administration of cyclohexylamine. The positive cyclophosphamide control group clearly differed from the untreated control and from the cyclohexylamine group in the parameters studied; the results were highly significantly different from those obtained in the untreated control group. The frequencies of the aberrant metaphases were 3.41%, including gaps, and 1.99% without gaps. The frequency of the translocations was 0.71% (5/704). Cyclohexylamine sulfate, administered five times at 150 mg/kg po, had no mutagenic effect, whereas cyclophosphamide, administered five times at 100 mg/kg po, had a chromosome-damaging effect on Chinese hamster spermatogonia. (26 refs)

214. HISTOLOGICAL EXAMINATION OF PERINATAL EYE DEVELOPMENT IN THE RAT AFTER INGESTION OF SODIUM CYCLAMATE AND SODIUM SACCHARIN DURING PREGNANCY.
Luckhaus G, Machemer L
Institut fur Toxikologie der Bayer AG, Postfach 101709, D5600 Wuppertal 1, W. Germany
Food Cosmet Toxicol; 16(1):7-11 1978

Pregnant female Wistar rats were fed a diet containing 5% sodium cyclamate or 0.4% sodium saccharin for 20 days after mating. The daily ingested dose was 1,495 mg for the cyclamate animals, 98.8 mg for the saccharin group. Examination of the fetuses on day 20 of pregnancy or the young at 3 wk of age revealed no histological changes in the lens, vitreous body, insertion of the optic nerve, or other parts of the eye. (11 Refs)

215. TERATOGENICITY OF CYCLOHEXYAMINE IN MAMMALS.
Becker BA, Gibson JE
Toxicol Appl Pharmacol; 5:551-552 1970

216. DETECTION OF CHEMICAL MUTAGENS BY THE DOMINANT LETHAL ASSAY IN THE MOUSE.
Epstein SS, Arnold E, Andrea J, Bass W, Bishop Y
Toxicol Appl Pharmacol; 23:288-325 1972

217. PRENATAL DEVELOPMENT IN THE RAT FOLLOWING ADMINISTRATION OF CYCLAMATE, SACCHARIN AND SUCROSE.
Fritz H, Hess R
Experientia; 24:1140 1968

218. TERATOGENICITY OF STRUCTURAL TRUNCATES OF CYCLOPHOSPAMIDE IN MICE.
Gibson JE, Becker BA
Teratology; 4:141-150 1971

219. EFFECTS OF CYCLOHEXYLAMINE ON THE FERTILITY OF MALE RATS.
Green S, Palmer KA, Legator MS
Food Cosmet Toxicol; 10:29-34 1972

220. REPRODUCTION STUDY IN RATS ORALLY TREATED WITH CYCLOHEXYLAMINE SULFATE.
Khera KS, Stutz DR, Gunner SW, Lyon DA, Grice HC
Toxicol Appl Pharmacol; 18:263-268 1971

221. THE TERATOGENIC AND EMBRYOTOXIC EFFECT OF CYCLAMATE, SACCHARIN AND SUCROSE.
Klotzsche C
Arzneim Forsch; 19:925-928 1969

222. THE MUTAGENICITY OF SODIUM SACCHARIN (S-NA). I. DOMINANT LETHAL TEST.
Masubuchi M, Takahashi A, Takahashi O, Yoshida S, Ando H, Kudo K, Hiraga K
Mutat Res; 54:218-219 1978

223. SACCHARIN, ITS POLLUTANTS AND THEIR TERATOGENIC EFFECT.
Lederer J
Louv Med; 96:495-501 1977

224. CYTOGENETIC AND TERATOGENIC EFFECT OF CYCLAMATE AND ITS METABOLITES.
Lederer J, Collin JP, Pottier-Arnould AM, Gondry E
Therapeutique; 47:357-363 1971

225. TOXIC AND TERATOGENIC EFFECT OF SODIUM CYCLAMATE ON THE DESCENDANTS OF GESTATING RATS AND MICE.
Lederer J, Pottier-Arnould AM
Journ Annu Diabetol Hotel Dieu; 331 1970

226. STUDIES ON CYCLAMATE AND SACCHARIN ON EMBRYOTOXIC AND TERATOGENIC EFFECTS IN THE MOUSE.
Lorke D
Arzneim Forsch; 19:920-922 1969

227. THE TOXICITY OF CYCLAMATE ON THE MOUSE EMBRYO.
Lorke D
Arzneim Forsch; 19:923-925 1969

228. THE EFFECT OF SEVERAL WEEKS TREATMENT ON MALE AND FEMALE MICE WITH SACCHARIN, CYCLAMATE OR CYCLOHEXYLAMINE ON FERTILITY AND DOMINANT LETHAL EFFECTS.
Lorke D, Machemer L
Humangenetik; 26:199-205 1975

229. METHOD FOR TESTING MUTAGENIC EFFECTS OF CHEMICALS ON SPERMATOGONIA OF THE CHINESE HAMSTER. RESULTS OBTAINED WITH CYCLOPHOSOPHAMIDE, SACCHARIN AND CYCLAMATE.
Machemer L, Lorke D
Arzneim Forsch; 25:1889-1896 1975

230. FEEDING AND REPRODUCTION OF RATS FED CALCIUM CYCLAMATE.
Nees PO, Derse PH
Nature (Lond); 208:81-82 1965

231. EXPERIMENTAL STUDIES ON CYCLOHEXYLAMINE IN RELATION TO CONGENITAL ANOMALIES.
Omori Y, Kuwamura T, Tanaka S, Nakaura S
EMS Newsl; 3:30 1970

232. INDUCTION OF DOMINANT LETHALS IN MICE BY SODIUM SACCHARIN.
Rao MS, Qureshi AB
Indian J Med Res; 60:599-603 1972

233. LD50 OF THE SACCHARIN OR CYCLAMATE FOR MICE EMBRYO IN THE 7TH DAY OF PREGNENCY (FETAL MEDIAN LETHAL DOSE: FLD50).
Tanaka R
J Iwate Med Assoc; 16:330-337 1964

234. THE TOXICITY OF ARTIFICIAL SWEETENERS TO EMBRYO.
Tanaka R
Jpn J Hyg; 11:1 1969

235. THE TOXICITY OF SYNTHETIC SWEETENING AGENTS TO MICE EMBRYOS.
Tanaka R
J Public Health Assoc; 11:909 1964

236. STUDIES ON THE TERATOGENICITY OF FOOD ADDITIVES. 2. EFFECTS OF CYCLOHEXYLAMINE AND CYCLOHEXYLAMINE SULFATE ON THE FETAI DEVELOPMENT IN RATS.
Tanaka S, Nakavra S, Kawashima K, Nagao S, Suwamura T, Omori Y
J Food Hyg Soc Jpn; 14:542-548 1973

237. COMBINED CHRONIC FEEDING AND THREE-GENERATION REPRODUCTION STUDY OF SODIUM SACCHARIN IN THE RAT.
Taylor JM, Friedman L
Toxicol Appl Pharmacol; 29:154 1974

B. Cytogenetic Effects

238. HOST-MEDIATED CYTOGENETIC ASSAY.
Brewen JG
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830
Mutat Res; 31(1):5-8 1975

A test which allows direct comparison of chromosome aberration production in prokaryotes and eukaryotes, as well as human cells, in the same environment is presented. The mutagenic events analyzed are structural alterations of the chromosomes. Leukocytes are isolated and purified and then put into a chamber which is put in a host animal. The host animal can be treated with the test compound at any stage of the leukocytes transformation and ultimate cell division. Mitotic cells are harvested from the chambers. This technique was used to test the clastogenic effects of methyl methanesulphonate and cyclohexylamine with mice and Chinese hamsters, respectively, being used as the hosts. Although the technique is initially cumbersome, it allows human cells to be used as target cells in an in vivo situation where detoxification of a compound, or metabolic conversion of a harmless compound into a mutagen, must be considered. (9 refs)

239. CYTOGENIC EFFECT OF CYCLAMATE ON HUMAN PERIPHERAL LYMPHOCYTES IN VIVO.
Bauchinger M, Schmid E, Pieper M, Zollner N
Radiobiol Inst. U. Munich, Germany
Dtsch Med Wochenschr; 95(44):2220-2223 1970

The side effects of the cyclamate sweeteners (sodium or potassium salts of cyclohexylsulfaminic acid) were investigated from the point of view of cytogenetic action. A chromosome analysis of peripheral lymphocytes was carried out on: a cyclamate group (3 women, 8 men) who had been placed on a cyclamate regimen due to liver or kidney disease; a control group I (3 women, 7 men) with similar diseases to those of the cyclamate group but on a regimen of fructose; and a control group II (14 women, 38 men) of healthy subjects. Both in the cyclamate group and in control group I, 48-hr cultures were obtained with an analysis of 100 cells; in the control group II 48- and 68-hr cultures were obtained. In the cyclamate group, a mean number of chromosomal aberrations was 3.3% of all evaluated cells, with a mean number of breaks/cell of 0.045, which was about 2 times higher than either control group. The chromosome aberration in the patients with liver disease was not due to a virus infection. However, these changes in the lymphocytes may not be a specific consequence of cyclamate.

240. CYTOGENETIC STUDIES WITH CYCLAMATE AND RELATED COMPOUNDS.
Stoltz DR, Khera KS, Bendall R, Gunner SW
Food Drug Directorate Res. Labs., Ottawa, Canada
Science; 167(3924):1501-1502 1970

Sodium cyclamate, cyclohexylamine sulfate, N-hydroxycyclohexylamine HCl (a metabolite of cyclohexylamine) and dicyclohexylamine sulfate (an occasional contaminant of cyclamate) induced chromosomal damage in cultures of human peripheral WBC. Most chromosomal aberrations were gaps and breaks. Exchange figures and unusual chromosomes of unknown derivation were infrequent, but observed only in treated cultures. The frequencies of chromosomal aberrations were essentially the same after 5 or 25 hours of exposure. These compounds had essentially the same effects on the chromosomes.

241. CYTOGENETIC EFFECTS OF CYCLOHEXYLAMINE AND N-OH-CYCLOHEXYLAMINE ON HUMAN LEUKOCYTES AND CHINESE HAMSTER BONE MARROW.
Brewen JG, Pearson FG, Jones KP, Luippold HE
Oak Ridge Nat. Lab., Tenn.
Nature (Lond); 230(9):15-16 1971

Short term human leukocyte cultures were exposed to 20, 100, or 500 microg/ml of cyclohexylamine (CHA) at the G0, G1, S, or G2 phase of the mitotic cycle; leukocytes were also exposed to 25, 50, 100, 200, or 250 micro/ml of N-hydroxycyclohexylamine (N-OHCHA) in all mitotic stages except the G0 phase. In related in vivo experiments, hamsters were given implanted diffusion chambers containing human leukocytes and treated with CHA. The hamsters were killed 60-66 hr after implantation and the diffusion chambers were withdrawn for examination. In none of the experiments was there an increase in the incidence of chromatid breaks occurring in CHA-treated or N-OHCHA-treated leukocytes. Asymmetric chromosome exchanges (including rings and dicentrics) were seen to have a very low frequency in treated and in untreated leukocytes.

242. CARCINOGEN-INDUCED CHROMOSOMAL BREAKAGE DECREASED BY ANTIOXIDANTS (MEETING ABSTRACT).
Shamberger RJ, Baughman FF, Kalchert SL, Willis CE, Hoffman GC
Cleveland Clin. Fdn., Ohio
Proc Natl Acad Sci USA; 70(5):1461-1463 1973

Blood leukocyte cultures were incubated with antioxidants and the carcinogens sodium cyclamate and 7,12-dimethylbenz(a)anthracene in different combinations. There were 17.4% more chromosomal breaks in the group of cells treated with dimethylbenzanthracene only than in the untreated controls. The reductions in chromosomal breaks by the antioxidants were as follows: ascorbic acid,31.7%; butylated hydroxytoluene, 63.8%; Na2Se03,42.0%; and dl-a-tocopherol,63.2%. Multiple chromosomal breaks were distributed equally throughout the experimental groups. Sodium cyclamate had only slightly more chromosomal breaks than the controls (11.6 compared to 10.9%). In the cyclamate groups treated with Na2Se03, 11.2% of chromosomes were broken. More acrocentric-type chromosomal breaks (21.7%) were seen in the untreated cells than the cells treated with cyclamate (3.4%) or dimethylbenz-anthracene alone (4.8%). The carcinogen-treated groups had a higher percentage of meta breaks than the untreated controls. The protection against chromosomal breakage by antioxidants appears to be consistent with epidemiological evidence that antioxidants prevent cancer. The anti-carcinogenic effect in

tissue culture, however, cannot be differentiated from mutagenic, teratogenic, or cytotoxic effects.

243. SACCHARIN: CYTOGENETIC EFFECT ON HUMAN LYMPHOCYTES IN VITRO (MEETING ABSTRACT).

Chang P, Stacey T
Dept. Biol., California State Coll., Pa.
Proc Pa Acad Sci; 48):50-51 1974

Chromatid aberrations were determined in human lymphocyte cultures incubated at 37 C with 0.002-2 mg/ml of sodium saccharin for 72 hr. Cultures containing low saccharin concentrations did not differ significantly from control cultures. At 2 mg/ml, saccharin produced chromosome gaps from control cultures. At 2 mg/ml, saccharin produced chromosome gaps and 18 chromosome breaks/66 cells; the percentage of breaks (27.2%) differed significantly from the control. Lymphocytes treated with 20 mg/ml of saccharin appeared distorted and did not undergo mitosis. Tripolar and tetrapolar divisions were not observed. The single chromatid breaks produced by saccharin are important in terms of mutagenicity and carcinogenicity. Assuming a daily average saccharin concentration of 0.002 mg/ml, it may take a constant consumer 3-5 yr to reach the in vivo concentration (2 mg/ml) at which there would be mutagenic or carcinogenic damage. However, experimental data on body absorption and the excretion rate of saccharin are needed.

244. CHROMOSOME TESTS WITH 134 COMPOUNDS ON CHINESE HAMSTER CELLS IN VITRO - A SCREENING FOR CHEMICAL CARCINOGENS.

Ishidate M, Odashima S
Dept. Chemical Pathology, Natl. Inst. Hygienic Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158, Japan
Mutat Res; 48(3/4):337-353 1977

Chromosome aberrations were investigated in Chinese hamster cells cultured with carcinogenic N-nitroso compounds and their related derivatives, food additives, medical drugs, pesticides and other common industrial and laboratory chemicals. Growth inhibition tests were carried out preliminary to chromosome tests. Of the 134 chemicals, 63 gave negative results in the chromosome aberration test even at doses which markedly inhibited cell growth. Nearly all compounds known to be mutagenic in bacteria were also positive in the chromosome aberration tests. Urethane and diethylstilbestrol, known to be carcinogenic but not mutagenic in bacteria, were positive. Compounds such as N-alkyl-N-nitroguanidines, barbital, sodium benzoate, saccharin sodium, sodium nitrite, sodium nitrate and 4-aminoquinoline-1-oxide were positive but were not conclusively tested for carcinogenicity. (16 Refs)

245. CHROMOSOME ABERRATION TESTS WITH CHINESE HAMSTER CELLS IN VITRO WITH AND WITHOUT METABOLIC ACTIVATION - A COMPARATIVE STUDY ON MUTAGENS AND CARCINOGENS (MEETING ABSTRACT). (P. 16)

Ishidate M
Natl. Inst. Hygienic Sciences, Tokyo, Japan
21st Congress of the European Society of Toxicology held in Dresden, E. Germany, 11-13 June 1979. European Society of Toxicology:, 194 pp., 1979.

Chromosome aberration tests in vitro have been used as a rapid and relatively sensitive method for the detection of possible mutagens and carcinogens in our environment. In our conventional system, Chinese hamster cells (CHL) were treated with different doses of the test chemical and chromosome preparations were made 24 hr and 48 hr after treatment. On activation, the cells were exposed to the chemical together with S-9 mix prepared from rat liver homogenate. From our screening data on 400 different chemicals, nearly half were positive, in which well-known carcinogens or mutagens were included. Carcinogenic N-nitrosocompounds were strongly positive either in the conventional or the activation system while benz(a)pyrene, quinoline, dimethylbenz(a)anthracene and some other procarcinogens induced aberrations only on activation. The incidence vs dose relationship seemed to be parallel to the incidence of revertants in Ames tests with bacteria among corresponding chemicals tested. However, carcinogens such as diethylstilbestrol, urethan, ethionamide, maleic anhydride, and other chemicals such as barbital, aspirin, acetaminophen, propyl gallate, sodium nitrite, sodium benzoate or saccharin sodium were only positive in our chromosome tests. (no Refs)

246. MUTAGENICITY TEST WITH SACCHARIN IN THE MALE MOUSE.

Leonard A, Leonard ED
Mammalian Genetics Lab., Dept. Radiobiology, C.E.N.-S.C.K., B-2400 MOL, Belgium
J Environ Pathol Toxicol; 2(4):1047-1053 1979

The ability of saccharin to induce chromosome aberrations in male C57BL mice was tested after acute (1, 2, or 4 g/kg ip) or chronic (20 g/liter in drinking water for 100 days) treatment. All in vivo tests on mice of both treatment groups were negative. The incidence of chromosome aberrations in the bone marrow cells was not increased, less than 4% RBC with micronuclei were found in treated and control mice, and there were no demonstrable effects on somatic or germ cells. In the acute study, 44% of females mated with control males and 27% of those mated with saccharin-treated males became pregnant during the first week (p less than 0.001); this difference was attributed to stress resulting from saccharin injection. The total number of dead embryos per pregnant female was significantly lower in the second- and third-week mating groups treated with saccharin than in the controls; the reason for this is not known. In the chronic experiment, the incidence of pregnancy among females mated to treated males was significantly greater (p less than 0.01) than that among the females mated to controls. It is concluded that the positive findings reported in the literature were probably due to the mutagenic activity of saccharin impurities. (17 Refs)

247. SACCHARIN: LACK OF CHROMOSOME-DAMAGING ACTIVITY IN CHINESE HAMSTERS IN VIVO.

van Went-de Vries GF, Kragten MC
Lab. Pharmacol., Natl. Inst. Public Health, Bilthoven, Netherlands
Food Cosmet Toxicol; 13(2):177-183 1975

Chromosomes in bone-marrow cultures from 20 Chinese hamsters given high doses of saccharin were studied. The test animals and a group of 20 controls were ip injected with 0.25 ml of pertussis vaccine, containing 16 x 109 bacteria/ml, to increase the population of mitotic cells. The animals were then given 1.5 g/kg/day of sodium saccharinate by gastric intubation on days 2, 3, and 4 after pertussis injection. The saccharin contained 6-7 impurities including 0.5% o-toluenesulphonamide . Phytohemagglutinin (PHA) was administered on day 6 and bone marrow cultures were taken on day 8 after pertussis injection. In each culture, 50 metaphases were analyzed. No statistically significant increases in the number of polyploid or aneuploid cells or in structural chromosome abnormalities were seen in comparison with the controls. Neither the saccharin nor its impurities caused chromsome abnormalities in this experiment, suggesting that saccharin has no in vivo chromosome-damaging effect on mitotic cells.

248. SACCHARIN-INDUCED SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER AND HUMAN CELLS.
Wolff S, Rodin B
Lab. Radiology, Univ. California, San Francisco, CA, 94143
Science; 200(4341):543-545 1978

The ability of the sodium salt of saccharin (lot S1022) and purified saccharin to induce sister chromatid exchanges (SCE's) in cultured Chinese hamster ovary cells and human lymphocytes was investigated. In the ovary cells, no growth was noted in cells treated with greater than or equal to 1.5% S1022 or with greater than 1.2% pure saccharin. In the lymphocytes, no growth was noted in cells treated with greater than 0.5% S1022 or pure saccharin. However, both batches of saccharin increased the yield of SCE's in both types of cells. These findings indicate that the weak carcinogen saccharin does induce cytogenetic changes in cultured cells. (14 Refs)

249. MONITORING OF GENETIC ENVIRONMENTAL RISK WITH NEW MUTAGENICITY TESTS.
Renner HW
Inst. Biochemistry, Federal Res. Center Nutrition, Engesserstrasse 20, D-7500 Karlsruhe, W. Germany
Ecotoxicol Environ Saf; 3(2):122-125 1979

Mammalian mutagenicity tests are discussed, including the dominant lethal test, the micronucleus test, the chromosome aberration test, and the sister chromatid exchange test. Difficulties encountered with these tests include the sensitivity of the test system, the selection of reliable methodologies for assessing the mutagenic activity, the interpretation of data and its extrapolation to man, the extent of synergistic effects between different chemicals, the role of comutagens, and the metabolic activation/detoxification of the compounds. Experiments with the sister chromatid exchange test have shown it to be at least 10-fold more sensitive than others. The genetic toxicity of various cytostatic agents (including cyclophosphamide, triaziquone, mitomycin C, bleomycin, and procarbazine) as determined by each of the mutagenicity tests is tabulated. The lowest effective dose of triaziquone in mg/kg body wt detectable by the dominant lethal test was 0.125 in mice, by the micronucleus test was 0.062 in Chinese hamsters, was 2 x 0.031 by the chromosome aberration test in Chinese hamsters, compared to 0.0001 in the in vivo sister chromatid exchange test in Chinese hamsters. Recent results using the new in vivo sister chromatid exchange test of saccharin and 2,4,5-trichlorphenoxyacetic acid are discussed. (no Refs)

250. CHROMOSOME ABERRATIONS AND SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER CELLS EXPOSED TO VARIOUS CHEMICALS.
Abe S, Sasaki M
J Natl Cancer Inst; 58:1635-1641 1977

251. THE EFFECTS OF SOME ARTIFICIAL SWEETENERS ON CROSSING OVER AND FECUNDITY IN DROSOPHILA MELANOGASTER.
Chinnici JP
Sci Biol J; 1:77-80 1975

252. CYCLAMATE AND CHA- LACK OF EFFECT ON THE CHROMOSOMES OF MAN.
Dick CE
Mutat Res; 26:199 1974

253. IN VITRO EFFECT OF CYCLAMATE ON HUMAN CHROMOSOMES.
Ebnezer LN, Sadasivan G
Q J Surg Sci; 6:116-118 1970

254. IN VITRO CYTOGENETIC INVESTIGATION OF CALCIUM CYCLAMATE, CYCLOHEXYLAMINE AND TRIFLUPROMAZINE.
Green S, Palmer KA, Legator MS
Food Cosmet Toxicol; 8:617-623 1970

255. EFFECT OF CYCLAMATE AND SACCHARIN ON THE CHROMOSOMES OF A CHINESE HAMSTER CELL LINE.
Kristofferson U
Hereditas; 70:271-282 1972

256. THE CYTOGENETIC AND TERATOGENIC EFFECT OF CYCLAMATE AND ITS METABOLITES.
Lederer J, Collin JP, Pottier-Arnould AM, Gondry E
Therapeutique; 47:357-363 1971

257. CYTOGENETIC STUDIES IN RATS OF CYCLOHEXYLAMINE, A METABOLITE OF CYCLAMATE.
Legator MS, Palmer KA, Green S, Petersen KW
Science; 165:1139-1140 1969

258. CHROMOSOME CHANGES IN MONGOLIAN GERBIL FOLLOWING CALCIUM CYCLAMATE ADMINISTRATION.
Majumdar SK, Solomon M
Nucleus; 14:168-170 1971

259. CYTOGENIC STUDIES OF CALCIUM CYCLAMATE IN MERIONES UNGUICULATUS (GERBIL) IN VIVO.
Majumdar SK, Solomon M
Can J Genet Cytol; 13:189-194 1971

260. LACK OF THE CYTOGENETIC EFFECTS OF SACCHARIN AND ITS IMPURITIES ON CHO-K1 CELLS.
Masubuchi M, Nawai S, Hiraga K, Hirokado M
Annu Rep Tokyo Metr Res Lab PH; 28:1590161 1977

261. CHROMOSOME LOSS INDUCED BY SACCHARIN FED TO DROSOPHILA.
Minter J, Mittler S
9th Annual Meeting of the Environmental Mutagen Society, March, San Francisco, 1978.

262. CYTOGENIC STUDIES OF CYCLOHEXYLAMINE, A METABOLITE OF CYCLAMATE.
Mostardi RA, Keller R, Koo R
Ohio J Sci; 72:313 1972

263. IN VITRO EFFECT OF SODIUM CYCLAMATE ON HUMAN CHROMOSOMES.
Perez Requejo JL
Sangre; 17:386-394 1972

264. CYTOGENETIC EFFECTS OF CYCLAMATES ON HUMAN CELLS IN VITRO.
Stone E, Lamson E, Chang US, Pickering KW
Science; 164:568-569 1969

265. CYCLOHEXYLAMINE, A CHROMOSOME ABERRATION INDUCING SUBSTANCE: NO TERATOGENICITY IN MICE.
Takano K, Suzuki M
Congenital Amomalies; 11:51-57 1971

266. SOME ASPECTS OF CYTOGENETIC EFFECTS OF SODIUM CYCLAMATE ON HUMAN LEUCOCYTES IN VITRO.
Tokumitsu T
Proc Jpn Acad; 47:635-639 1971

C. Mutagenicity Studies

267. AMES TEST SUCCESS PAVES WAY FOR SHORT-TERM CANCER TESTING.

Fox JL

Chemical Engineering News, 1155 16th St., NW, Washington, DC

Chem Eng News; 55(50):34-36,42,44-46 1977

The Ames Salmonella typhimurium assay and other short-term screening tests for chemical carcinogens and mutants are evaluated. Data are presented on the carcinogenicity of saccharin as evaluated by a battery of tests, including the Ames assay; the Pol test with DNA repair-deficient bacteria; the Drosophila test; tests using unscheduled DNA synthesis, sister chromatid exchange, mutations in cultured mammalian cells, and animal cell transformation; and the plasminogen activator test. (no Refs)

268. NON-MUTAGENICITY OF SACCHARIN (LETTER TO EDITOR).

Pool B

Inst. Toxicology and Chemotherapy, German Cancer Res. Center, Im Neuenheimer Feld 280, 69 Heidelberg, W. Germany

Toxicology; 11(1):95-97 1978

Assay of the mutagenicity of a relatively pure sample of sodium saccharin (less than 10 ppm o-toluolsulfonamide) in Salmonella typhimurium TA1535, TA1537, TA98, and TA100 produced negative results. Previous positive responses may have been due to impurities. (10 Refs)

269. MUTAGENICITY STUDIES OF COMMERCIALLY AVAILABLE SACCHARINS (MEETING ABSTRACT).

Majumdar SK, Viglianti GA, Thatcher JD, Dennis EH, Maharam LC, Natoli J

Dept. Biology, Lafayette Coll., Easton, PA, 18042

Can J Genet Cytol; 20(3):449 1978

Three widely used and commercially available saccharin preparations were studied to evaluate their mutagenic properties in three strains of Salmonella typhimurium (TA 98, TA 100 and TA 1535) both in the presence and absence of a mouse liver homogenate (S9). No detectable mutagenicity was expressed by any of these saccharins on any tested strains. Only one saccharin brand was used to determine the effects of the chemical on the bone-marrow chromosomes of mice in vivo. This preparation did not produce any significant increase of chromosome breaks, gaps or fragments over the control level. (no Refs)

270. SACCHARIN AND OTHER SWEETENERS: MUTAGENIC PROPERTIES.

Batzinger RP, Ou SL, Bueding E

Dept. Pathobiology, Johns Hopkins Medical Inst., Baltimore, MD 21205

Science; 198(4320):944-946 1977

The mutagenic activities of saccharin, neohesperidin dihydrochalcone (NHDC), and xylitol were determined directly, by using bacterial tester strains Salmonella TA100 and TA98 in a host-mediated assay, and in the urine of the test mice after oral administration of the test substances. Five saccharin preparations were tested. After the oral administration of three of the saccharin preparations, significant mutagenic activities in the urine were detectable with both Salmonella strains. In the Ta100 strain the mutagens were inactivated by liver microsome preparations while the mutagenic effects of the urine were enhanced in the TA98 strain by the same treatment leading to the conclusion that two different mutagenic substances were present. No mutagenic activity was found with TA98 in the urine of mice treated with highly purified saccharin. There was low but significant activity with the TA100 strain. The urine from mice given highly purified saccharin contained a promutagen which apparently was masked by the greater mutagenic activity of the other urine. Urine of animals treated with xylitol or NHDC exhibited no mutagenic activity with either TA100 or TA 98. (13 Refs)

271. THE APPLICATION OF SHORT-TERM MICROBIAL MUTAGENICITY TESTS IN THE IDENTIFICATION AND DEVELOPMENT OF NON-TOXIC, NON-ABSORBABLE FOOD ADDITIVES (MEETING ABSTRACT).

Brown JP, Brown RJ, Roehm GW

Dynapol, Palo Alto, CA, 94304

Mutat Res; 53(2):158 1978

Microbial mutagenicity tests, particularly the Salmonella typhimurium/microsome assay, have become an integral part of research and development efforts to bring new, potentially safe food additives to the market. The tests are currently being employed in three product areas: water-soluble food dyes and oil-soluble anti-oxidants, both based on high polymer technology, and non-absorbable synthetic sweeteners. In about 2 yr of testing over 400 individual chemicals have been screened for mutagenicity with the Salmonella/microsome assay. The types of test applications are well illustrated by our polymeric dye program. In this area a few hundred chromophores, intermediates and possible degradation products have been screened by chemical class: viz; anthraquinones (110); anthrapyridones (40); anthrapyridones (20); benzanthrones (25); azo dyes (30); naphthalimides and naphthalic anhydrides (14); triphenylmethane and xanthene dyes (10). The results of such tests have provided invaluable guidelines for chromophore selection. The assay has also proved useful at subsequent stages of development where raw materials, synthetic mixtures, effluents and ultrafiltrates are readily monitored. Polymeric materials have been tested after thermolytic and after photolytic stress in simulated food product environments. In addition to activation by mammalian microsomes, polymers are subjected to anaerobic plate assays supplemented with enzyme extracts of rat cecal microorganisms. Urine from test animals receiving acute or subchronic oral doses of polymeric dyes are tested following deconjugation with beta-glucuronidase and/or sulfatase in addition to microsomal activation. While the relatively high volume screening type tests are performed with the standard set of Salmonella tester strains (TA1535, TA100, TA1537, TA1538, TA98), more detailed tests can be performed on the relatively few product candidates selected for further development. At present these tests include point mutations and chromosomal effects in Saccharomyces cerevisiae D7, and DNA repair and fluctuation tests in Salmonella and Escherichia coli. (no Refs)

272. THE MUTAGENICITY OF SACCHARIN IMPURITIES. I. DETECTION OF MUTAGENIC ACTIVITY.

Stoltz DR, Stavric B, Klassen R, Bendall RD, Craig J

Toxicology Res. Div., Health Protection Branch, Tunney's Pasture, Ottawa, Canada K1A 0L2

J Environ Pathol Toxicol; 1(1):139-146 1977

Sodium saccharin, o-toluenesulfonamide, and impurities extracted from commercial saccharin by water and organic solvents were tested for mutagenicity with Salmonella typhmurium. The organic solvent-soluble impurities exhibited strong mutagenic activity for TA98 and slight activity for TA100. Mutagenic activity for S. typhimurium TA98 was demonstrated in extracts of some but not all sodium saccharin samples produced by both the Maumee and Remsen-Fahlberg processes. The relevance of the mutagenic impurity to the carcinogenicity of saccharin is discussed. (11 Refs)

273. DETECTION OF MUTAGENIC IMPURITIES IN CARCINOGENS AND NONCARCINOGENS BY HIGH-PRESSURE LIQUID CHROMATOGRAPHY AND THE SALMONELLA/MICROSOME TEST.

Donahue EV, McCann J, Ames BN
Dept. Biochemistry, Univ. California, Berkeley, CA 94720
Cancer Res; 38(2):431-438 1978

High-pressure liquid chromatography (HPLC) was used in combination with the Salmonella/microsome test to detect small amounts of mutagenic impurities in 11 carcinogens and noncarcinogens. The mutagenicity of each of the 11 chemicals was compared before and after purification by HPLC, and in four cases there was a significant change in the mutagenic activity after purification. In the case of 7-hydroxy-2-acetylaminofluorene (7-OH-2-AAF), the purified chemical was virtually nonmutagenic. With bis-2,7-acetylaminofluorene and 7-methylbenz(a)anthracene direct mutagenic activity was lost following purification, but activity was retained in the presence of a rat liver microsomal preparation. The mutagenic potency of 2-aminobiphenyl (2-AB) decreased but did not disappear. The impurity in 7-OH-2-AAF that is responsible for its mutagenicity is probably the potent carcinogen 2-acetylaminofluorene; 4-aminobiphenyl is probably the mutagenic impurity in 2-AB. For industrial chemicals, which often contain fairly large amounts of impurities, the Salmonella test could be used in the design of industrial syntheses and as a batch process monitor, to minimize the introduction of mutagenic impurities. It has also been found that impurities in saccharin (20 ppm of as yet unidentified impurities) are mutagenic in the Salmonella test. Thus, it is possible that the carcinogenicity of saccharin could be due to a potent carcinogenic impurity. (43 Refs)

274. SACCHARIN: AN EPIGENETIC CARCINOGEN/MUTAGEN?

Ashby J, Styles JA, Anderson D, Paton D
Central Toxicology Labs., Imperial Chemical Industries Ltd., Alderley Park, Macclesfield, Cheshire, England
Food Cosmet Toxicol; 16(2):95-103 1978

The carcinogenicity of saccharin (Sa), sodium saccharin (SSa), and 13 related compounds was evaluated in two in vitro tests, and the results were evaluated within the context of the ability of commercial Sa to cause bladder cancer in rats and dominant lethal effects in mice. Five doses (4-2,500 ug/plate) of the test compounds were used in the Salmonella assay. In the cell-transformation assay, baby hamster kidney cells in semisolid agar were exposed to six doses (0.025-2,500 ug/ml) of each compound. Except for 3-dimethylamino-psi-saccharin (DMASa), all compounds were negative in all four Salmonella tester strains used. DMASa had a positive effect in TA98 and TA100, but these results could not be reproduced. All compounds were negative in the transformation assay and all had a similar low toxicity. The following hypotheses are proposed for the divergence between the in vitro and in vivo findings: (1) an undefined impurity in commercial Sa that is responsible for the carcinogenic effect is unable to produce positive effects in vitro because of its low concentration in the test material; (2) the electrophilic theory of DNA attack linked to the somatic mutation theory of cancer induction may not include all organic carcinogens (Sa is nucleophilic). Based on available evidence, it is suggested that the in vivo effects of commercial Sa are probably due to Sa per se and that they may arise by an epigenetic mechanism. Further, these effects may only be exhibited above a given threshold dose that may be much higher than the "safe" level suggested by analogy with carcinogens operating via a genotypic mechanism. (60 Refs)

275. DISSOCIATION OF MUTAGENIC FROM CHEMOTHERAPEUTIC ACTIVITIES OF DRUGS.

Batzinger RP
Johns Hopkins Univ., Baltimore, MD
Diss Abstr Int B; 39(10):4838 1979

The sensitivity and reproducibility of the Salmonella typhimurium mutagenicity test of Ames (1975) was increased by placing the required nutrients in the bottom rather than the top agar phase and by altering their concentrations. Since qualitatively and quantitatively different results were obtained with strains obtained from eight laboratories, attempts were made to stabilize reisolated strains by various culturing and storage techniques. As a result, these modifications enhanced the mutagenic responses of tester strains TA100 and TA98 to a number of mutagens. Commercially available preparations of saccharin exhibited significant mutagenic effects to varying degrees for S typhimurium both in vitro and in vivo. A purified preparation of saccharin was not mutagenic in the direct assay, but gave rise to mutagenic metabolites in the urine following administration to mice. Hence, it would appear that the impurities of saccharin could account for most, but not all, of the mutagenic activity. By marked contrast two other sweeteners, neohesperidin dihydrochalcone and xylitol exhibited no mutagenic activity neither in vivo nor in vitro. Recent reports indicate that the carcinogenic activity of benzo(a)pyrene was reduced by the administration of phenolic antioxidants, eg, t-butylhydroxyanisole (BHA), or ethoxyquin. These anticarcinogenic effects were paralleled in this study by a marked decrease in the mutagenic activities of the urines of mice treated with benzo(a)pyrene. It was also found that inclusion of BHA in the diet significantly reduced the mutagenic activity of four antischistosomal agents, hycanthone, IA-4 N-oxide, metrifonate and praziquantel, as well as of the anthelmintic, mebendazole and the sedative, diazepam. Urines collected from human subjects treated with either hycanthone, oxamniquine, praziquantel, metronidazole or CGP 4540 exhibited mutagenic activity to varying degrees when tested with strains TA98 and TA100. (no Refs)

276. MUTAGENIC EFFECTS OF SACCHARIN ON ASPERGILLUS NIGER.

Das A
Dept. Microbiology, Bose Inst., 93/1 Acharya Prafulla Chandra Road, Calcutta 700009, India
J Gen Microbiol; 114(part1):221-222 1979

Colonies of Aspergillus niger grown in medium containing saccharin at concentrations of 3 or 7 mg/ml were delayed in initiation of germination and showed increased numbers of morphological variants; further, the auxotrophic mutants had specific growth requirements. The results indicated that saccharin has a mutagenic effect on the cells of A niger, and it was inferred that there may be a risk of genetic damage when living cells are fed saccharin. (7 Refs)

277. GENETIC EFFECTS OF IMPURE AND PURE SACCHARIN IN YEAST.

Moore CW, Schmick A
Dept. Radiation Biology and Biophysics, Univ. Rochester, Rochester, NY, 14642
Science; 205(4410):1007-1010 1979

The effects of pure and impure saccharin on mitotic and intragenic recombination and reverse mutation in Saccharomyces cerevisiae were studied, and the extents to which these genetic events are affected by impure saccharin produced by two different processes were compared. The diploid strain CM-1293 of S. cerevisiae was incubated in medium containing 0, 2, or 20 mg of saccharin A (impure Maumee process saccharin), B (impure Remsen-Fahlberg

process) or C (purified from the same B batch). Dose-dependent increases were observed in the frequencies of abnormal cells. The frequency of aberrant types was saccharin A greater than saccharin B greater than saccharin C. Such aberrant cell types were not observed in cultures grown in medium without saccharin. Intergenic exchanges between homologous chromosomes were 11-12 times more frequent in cells grown in the presence of the lowest dose of impure saccharins than in cells grown without saccharin. Half as many exchanges occurred among cells grown with the low dose of saccharin C. At all three concentrations, cells grown in the presence of saccharin B showed higher frequencies of mitotic crossing over or gene conversion than cells grown in saccharin C. Saccharin A usually caused larger increases in both recombination and mutation than saccharins B and C, indicating the greater potential mutagenicity of saccharin A. It is concluded that the impurities in saccharin caused some or all of the observed genetic effects. However, the impurities would have to be potent to account for all the effects of saccharin and, therefore, saccharin per se or its metabolites might cause the effects. (19 Refs)

278. RECOMBINOGENICITY AND MUTAGENICITY OF SACCHARIN IN SACCHAROMYCES CEREVISIAE.

Moore CW, Schmick A
Dept. Biology, Univ. Rochester, Rochester, NY
Mutat Res; 67(3):215-219 1979

Diploid yeast (Saccharomyces cerevisiae) grown in the presence of a commercial lot of saccharin exhibited reproducible, dose-dependent increases in intergenic and intragenic recombination and mutation. Cells grew to nearly the same titer in media without saccharin and media containing 2 or 20 mg saccharin/ml, although cell viability was somewhat reduced in saccharin-containing media. At the high test dose of 100 mg/ml, titers and cell viability were more markedly lowered. Differences between this study and previous (negative) tests of saccharin in yeast are described. (20 Refs)

279. VALIDATION AND CHARACTERIZATION OF THE L5178Y/TK+/- MOUSE LYMPHOMA MUTAGEN ASSAY SYSTEM.

Clive D, Johnson KO, Spector JF, Batson AG, Brown MM
Genetic Toxicology Lab., Burroughs Welcome Co., Research Triangle Park, NC, 27709
Mutat Res; 59(1):61-108 1979

A specific-locus mutagenicity assay using L5178Y mouse lymphoma cells rendered heterozygous at the normally diploid thymidine kinase (TK) locus and supplemented with an exogenous in vitro metabolic activation system was validated. Validation took the form of dose-response data for 43 chemicals, including mutagens and carcinogens of varying potencies and several agents designed for human exposure. Mutagenicity and cytotoxicity in the presence or absence of noninduced and/or Aroclor-induced rat liver S-9 mix were compared for most of the chemicals. Twenty-five chemicals for which usable carcinogenicity data exist were used to construct an approx linear relationship between oncogenic potency in vivo and mutagenic potency in this system in vitro; linearity between these two endpoints extended over A greater than 100,000-fold range in potencies. Natulan, sodium saccharin, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene dimethylnitrosamine, diethylnitrosamine, and diethylstilbestrol, which are either negative or difficult to detect in the standard Ames assay, were mutagenic in this mammalian cell system. Characterization of the TK-/- mutants suggested that two mutagenic mechanisms contribute to their final yield. Large colony TK-/- mutants probably represent point or gene mutations affecting the TK locus. In addition, a class of small colony TK-/- mutants was described and characterized as being heritably growth-deficient; this and other properties suggest that these small colony TK-/- mutants originate by a heritable and viable chromosomal aberration. Most carcinogens and mutagens tested produced both classes of TK-/- mutants in this system; the relative proportions of small and large colony mutants were both mutagen- and dose-dependent. Comparative studies at the rapidly expressing TK locus and the slowly expressing hypoxanthine-guanine phosphoribosyltransferase (HGPRT) locus in these cells showed that several carcinogens detected at the TK locus are non- or very weakly mutagenic at the HGPRT locus. This is consistent with the induction of slow-growing specific locus mutants by a chromosomal mechanism and their subsequent dilution during this long expression time. (47 Refs)

280. CARCINOGENESIS TESTING OF SACCHARIN. NO TRANSFORMATION OR INCREASED SISTER CHROMATID EXCHANGE OBSERVED IN TWO MAMMALIAN CELL SYSTEMS.

Saxholm HJ, Iversen OH, Reith A, Brogger A
Inst. of Pathology, Univ. Oslo, Rikshospitalet, Oslo 1, Norway
Eur J Cancer; 15(4):509-513 1979

Saccharin was assayed in two mammalian cell systems for possible transforming or mutagenic effects. In mouse embryo fibroblast C3H/10T1/2 cells, saccharin was without transforming effects over a large concentration range. In 7,12-dimethylbenz(a)anthracene-transformed, but nononcogenic C3H/10T1/2 type I cells, saccharin had a slight effect on transition to the growth pattern morphology of types II and III cells, but this was not accompanied by characteristic changes in plasma membrane structure, as studied by scanning electron microscopy. Saccharin did not induce any sister chromatid exchange in human lymphocytes. Addition of a metabolic activation system (S-9 mix) did not change the sister chromatid exchange pattern, as usually seen after 3,4-benzopyrene treatment. Based on these studies, saccharin is neither a carcinogen nor a mutagen. (21 Refs)

281. MUTAGENICITY OF SACCHARIN IN DROSOPHILA: THE POSSIBLE ROLE OF CONTAMINANTS.

Kramers PG
Natl. Inst. Public Health, Bilthoven, Netherlands
Mutat Res; 56(2):163-167 1977

The mutagenicity of two saccharin samples and of two commonly occurring impurities of saccharin, o-toluenesulfonamide and p-toluenesulfonamide was determined in the Drosophila test for sex-linked recessive lethal mutations. The two saccharin samples had been prepared by the same company (Sherwin-Williams) and by the same process (Maumee), a fact that was not known at the beginning of the experiment. The saccharin (5 or 25 mM) and the impurities (5 mM) were administered to the Drosophila by abdominal injection (0.2 ul/fly) or by a 3-day feeding. One of the saccharin samples enhanced mutation frequency compared with controls. Although the increase was small and somewhat variable, it was reproducible and consistently restricted to brood A, implicating mature sperm as the sensitive germ cells. This sample was tested over a period of 16 mo, and there was a tendency for the mutation frequency to decrease with time. This might be due to the decomposition of the (unknown) mutagenic component of the sample. The other saccharin sample and the impurities were negative. In spite of their similar origin, the different mutagenic activities of the two saccharin samples can still be explained by general differences between lot numbers or by the fact that the mutagenic sample was prepared more recently than the nonmutagenic one. This would fit the supposition that the mutagenic contaminant is a rather unstable compound. (10 Refs)

282. FAILURE TO DETECT MUTAGENICITY BY INJECTION OF CYCLOHEXYLAMINE AND N'-HYDROXYCYCLOHEXYLAMINE INTO DROSOPHILA.
Browning LS
EMA Newsl; 6:18-19 1972

283. THE MUTAGENICITY OF CYCLAMATES AND THEIR METABOLITES.
Cattanach BM
Mutat Res; 39:1-28 1976

284. MUTAGENICITY TEST OF THE METABOLIC DERIVATIVES OF CYCLAMATE IN MAMMALIAN CELL CULTURES.
Chu EYH, Bailiff EG
EMS Newsl; 3:39 1970

285. VALIDATION AND CHARACTERIZATION OF THE L5178Y/TK/-MOUSE LYMPHOMA MUTAGEN ASSAY SYSTEM.
Clive D
Mutat Res; 59:61-108 1979

286. EVALUATION OF A DNA POLYMESASE-DEFICIENT MUTANT OF E. COLI FOR THE RAPID DETECTION OF CARCINOGENS.
Fluck ER
Chem Biol Interact; 15:219-231 1976

287. LACK OF MUTAGENICITY OF THE CYCLAMATE METABOLITES IN DROSOPHILA.
Knaap AG, Kramers PG, Sobels FH
Mutat Res; 21:341-344 1973

288. OBSERVATIONS OF MUTAGENIC PROPERTIES OF CYCLAMATES IN MAMMALS. (TRANSLATED TITLE)
Leonard A, Linden G
C R Seance Biol Fifiales; 116:468-469 1972

289. MUTATION TEST OF CALCIUM CYCLAMATE IN DROSOPHILA MELANOGASTER.
Majumdar SK, Freedman C
Drosophila Inf Serv; 46:114 1971

290. PRESENCE OF UNSCHEDULED DNA SYNTHESIS IN CULTURED HUMAN CELLS AFTER TREATMENT WITH SODIUM SACCHARIN.
Ochi H, Tonomura A
Mutat Res; 54:224 1978

291. INDUCTION OF MUTATIONS IN D. MELANOGASTER WITH O-SULPHOBENZOIC IMIDE (SACCHARIN).
Samuel BC, Rao MS
Drosophila Inf Serv; 48:47-49 1972

292. THE MUTAGENIC EFFECT OF ONE OF ARTIFICIAL SWEETENERS - SACCHARIN.
Sram R, Weidenhofferova H
Drosophila Inf Serv; 44:120 1969

293. MUTAGENIC ACTIVITY OF SACCHARIN.
Sram R, Audova
EMS Newsl; 6:25 1972

294. REACTION OF DROSOPHILA MELANOGASTER TO FOOD SUBSTANCES CONTAINING SODIUM CYCLAMATE, CALCIUM CYCLAMATE AND SODIUM SACCHARIN.
Stitch RB, Bannister NL, Jemison EW
Va J Sci; 21:116 1970

295. CYCLOHEXYLAMINE MUTAGENICITY: AN IN VIVO EVALUATION UTILIZING FETAL LAMBS.
Turner JH, Hutchinson DL
Mutat Res; 26:407-412 1974

296. MUTAGENICITY TESTING OF CYCLAMATES AND SOME PESTICIDES IN DROSOPHILA.
Vogel E, Chandler JLR
Experientia; 30:621-623 1974

297. COMPARATIVE RESULTS OF SHORT-TERM IN VITRO AND IN VIVO MUTAGENICITY TREST OBTAINED WITH SELECTED ENVIRONMENTAL CHEMICALS.
Wild D, Edkhardt K, Gocke E, King MT
International Symposium on Short-term Mutagenicity Test Systems for Detecting Carcinogens, Dortmund, FRG, November, 1978.

VII. SYNTHESIS AND ANALYSIS OF ARTIFICIAL SWEETENERS

298. THE THERMAL ENERGY ANALYSIS OF SODIUM SACCHARIN.
Krull IS, Goff U, Wolf M, Heos AM, Fine DH, Arsenault GP
Cancer Res. Div., Thermo Electron Corp., 45 First Ave., Waltham, MA, 02154
Food Cosmet Toxicol; 16(2):105-110 1978

A study to determine the presence of any N-nitroso compounds in a commercial sample of sodium saccharin was performed. A positive response of approx 0.0001 moles of an N-nitroso compound was detected using thermal energy analysis. This weak response is attributed to the decomposition of sodium saccharin itself and not to an N-nitroso impurity. (38 Refs)

299. THE REACTION OF CYCLOHEXYLSULFAMIC ACID (CYCLAMATE) WITH NITROUS ACID IN AQUEOUS HCL SOLUTION, ISOLATED HUMAN GASTRIC JUICE, AND URINE.
Kinawi A, Kia H
Arbeitsgruppe Umweltmutagene, Institut fur Biochemie und Molekularbiologie der Freien Universitat, Ostpreussendamm 111, D-1000 Berlin 45, W. Germany
J Clin Chem Clin Biochem; 16(6):365-369 1978

The pH dependency of the formation and decomposition of N-nitroso derivatives produced through the reaction of cyclohexylsulfamic acid with nitrous acid was examined by means of continuous photometric measurements of changes in absorbance. A strong pH dependence was observed for both the formation and decomposition reactions in an aqueous HCl solution. Between pH 1.09 and 1.58 both reactions demonstrated maximal rates, whereas at pH 2.61 the decomposition reaction had a half-time of 11.8 min. The increased reaction rate in this region was not solely due to an increase in the nitrite concentration of the medium, but also due to the change in pH as a result of the sulfuric acid breakdown product. The N-nitroso derivatives demonstrated a relatively high stability at pH 4.5. The reaction of cyclohexylsulfamic acid in isolated human gastric juice and urine showed the same pH dependency as the reaction in aqueous HCl solution. It is suggested that traces of the N-nitroso derivatives formed in the stomach enter a physiological stabilizing pH region. In addition, the cyclohexylsulfamic acid that is excreted in an unchanged condition probably reacts with nitrite, which originates as a product of nitrate reduction. (23 Refs)

300. STUDIES ON THE FORMATION OF CYCLOHEXYLAMINE AND N-METHYLCYCLOHEXYLAMINE FROM BROMHEXINE IN ANIMALS AND MAN, AND SIMULTANEOUS DETERMINATION OF CYCLOHEXYLAMINE AND N-METHYLCYCLOHEXYLAMINE BY GAS CHROMATOGRAPHY.

Matsumura R, Kohei H
Boehringer Ingelheim GmbH, Pharma Res. Japan, 103, Takada, Yato, Kawanishi, Hyogo-ken, 666-01, Japan
J Chromatogr; 117(2):383-391 1976

In order to detect cyclohexylamine and N-methylcyclohexylamine simultaneously in urine, a gas chromatographic method was developed in which Chromosorb 103 (a porous polymer) was found to be suitable as the column packing. The detection limits were 0.1 ug/ml of cyclohexylamine and 0.4 ug/ml of N-methylcyclohexylamine in urine. In tests on eight male Sprague-Dawley rats and eight male Himalayan rabbits, administered bromhexine (10 or 20 mg/kg, ip), which contains N-methylcyclohexylamine as part of its side-chain, neither cyclohexylamine nor N-methylcyclohexylamine was detected in the urine. The urine of five patients taking bromhexine continuously was similarly analyzed, and neither compound was found.

301. THIN LAYER CHROMATOGRAPHY FOR DETECTION OF ACESULFAM, SACCHARIN AND CYCLAMATE.

von Rymon Lipinski GW, Brixius HC
Hoechst Aktiengesellschaft, D-6230 Frankfurt/Main 80, W. Germany
Z Lebensm Unters Forsch; 168(3):212-213 1979

A method for separation and detection of Acesulfam-K (a synthetic sweetener: 6-methyl-1,2,3-oxathiazine-4(3H) one-2,3-dioxide), cyclamate, and saccharin by thin layer chromatography is described. The relative fronts obtained were 0.43, 0.56, and 0.72, respectively. Polyamide plates and a solvent system of xylol, n-propanal, and formic acid (5:5:1) were used, 2,7-Dichlorfluorescein in methanol is sprayed on dry plates to make the compounds visible in UV light. (2 Refs)

302. USES AND METABOLIC EFFECTS OF XYLITOL - PART I.

Fratzke AR, Reilly PJ
Dept. Chemical Engineering and Nuclear Engineering, Iowa State Univ., Ames, IA 50011
Process Biochem; 12(7):27-29 1977

The physical properties of xylitol and its breakdown in the body are described. Xylitol is produced from D-xylose, which is obtained by acid hydrolysis of xylans found in monocotyledons, hardwoods, agricultural plant wastes, and by specific hydrolysis with xylanase enzymes. Hydrogenation of xylose to xylitol is accomplished at temperatures ranging from 100 C to 140 C, at hydrogen pressures of 50 atmospheres, and in the presence of Raney nickel or other metal catalysts. Xylitol is stable to degradative rearrangements, oxidations, and elevated temperatures. This stability is apparent under neutral to basic conditions. The level and quality of sweetness ascribed to xylitol is superior when compared to other sugars and sugar alcohols. Gastrointestinal absorption of xylitol increases the rate of liver metabolism of xylitol. Cell metabolism of xylitol occurs along the glucuronic acid pathway and is localized in the liver. It appears that xylitol may be important for possible nutritive and sweetening use, as it possesses anticariogenic properties. (32 Refs)

303. MAUMEE MOVES CLOSER TO OPTIMUM PROCESS TO MAKE SACCHARIN.

Anonymous
Chem Eng News; 76-78 1963

304. PREPARATION OF PROPERTIES OF SOME N-SUBSTITUTED SULFAMIC ACIDS.

Audrieth LF, Sveda M
J Org Chem; 9:89-101 1944

305. NONCALORIC SWEETENERS: THEIR POSITION IN THE SWEETNER INDUSTRY. (P. 1)

Ballinger RA
Agricultural Economic Report No. 113. U.S. Department of Agriculture, Washington, D.C., 1967.

306. SWEETENERS, NON-NUTRITIVE.

Beck KM
Encyclopedia of Chemical Technology, 2nd edition. Kirk RE, Othmer DF, ed. John Wiley and Sons, New York, Vol. 19, pp. 598-607, 1960.

307. IDENTIFICATION AND QUANTITATIVE DETERMINATION OF SACCHARIN IN BIOLOGICAL FLUIDS.

Couch MW, Das NP, Scott KN, Williams CM, Foltz RL
Biochem Med; 8:362-370 1973

308. THE QUANTITATIVE DETERMINATION OF ORTHOTOLUENE SULFONAMIDE (O-TS) IN SACCHARIN BY U.V. SPECTROPHOTOMETRY AND BY GAS CHROMATOGRAPHY.

Jacin H
Dtsch Lebensm Rundsch; 71:428-429 1975

309. DETERMINATION OF ORTHOTOLUENESULFONAMIDE (O-TS) IN SOLUBLE SACCHARIN.

Janiak RA, Damon HH, Mohr TC
J Agric Food Chem; 26:710-711 1978

310. O-TOLUENESULFONAMIDE IN SACCHARIN PREPARATIONS.

Stavric B, Klassen R
J Assoc Off Anal Chem; 58:427-432 1975

311. IMPURITIES IN COMMERCIAL SACCHARIN. I. IMPURITIES SOLUBLE IN ORGANIC SOLVENTS.

Stavric B, Klassen RD, By AW
J Assoc Off Anal Chem; 59:1051-1058 1976

312. SWEETENER ECONOMICS.

Walter BJ
Symposium Sweeteners. Inglett GE, ed. Avi Publishing Company, Westport, Conn., pp. 47, 1974.

313. PRACTICAL CONSIDERATIONS FOR SYNTHETIC SWEETENERS: PAST, PRESENT AND FUTURE-CYCLAMATES.

Wiegand RG
Sweeteners and Dental Caries. Shaw JH, Roussos GG, ed. Information Retrieval, Inc., Arlington, Virginia, pp. 263-267, 1978.

314. SODIUM SACCHARIN PELLETIZED - NON-NUTRITIVE SWEETENER.

Anonymous
Sodium Saccharin Pelletized - Non-Nutritive Sweetener, Technical Data Sheet 3. The Sherwin-Williams Company, Chemical Division, Cleveland, Ohio, 1978.

315. SACCHARIN INSOLUBLE POWDER FCC - NON-NUTRITIVE SWEETENER.

Anonymous
Saccharin Insoluble Powder FCC - Non-Nutritive Sweetener, Technical Data Sheet 2. The Sherwin-Williams Company, Chemical Division, Cleveland, Ohio, 1978.

316. SODIUM SACCHARIN - NON-NUTRITIVE SWEETENER.
Anonymous
Sodium Saccharin - Non-Nutritive Sweetener, Technical Data Sheet 1. The Sherwin-Williams Company, Chemica Division, Cleveland, Ohio, 1977.

317. IMPORTS OF BENZENOID CHEMICALS AND PRODUCTS.
U.S. International Trade Commission
Imports of Benzenoid Chemicals and Products. U.S. International Trade Commission, Washington, D.C., USITC Publication 900, pp. 94, 1978.

318. SACCHARIN FROM JAPAN AND THE REPUBLIC OF KOREA.
U.S. International Trade Commission
Saccharin from Japan and the Republic of Korea. U.S. International Trade Commission, Washington, D.C., USITC Publication 846, pp. 61, 1977.

VIII. EVALUATION OF HEALTH BENEFITS OF ARTIFICIAL SWEETENERS

319. BENEFITS OF SACCHARIN: A REVIEW.
Rosenman K
Environmental Sciences Lab., Mt. Sinai Sch. Medicine, New York, NY, 10029
Environ Res; 15(1):70-81 1978

A review of the benefits of saccharin is presented. The most important aspect of treatment of adults with diabetes, most of whom are overweight, is control of caloric intake to reduce body wt. Use of artificial sweeteners is not recommended to reduce the possibility of a hyperglycemic peak in these patients. The only use of artificial sweeteners is for diabetic patients who need an inducement to adhere to a diabetic diet, or have an insatiable urge for sweets. However, no relation between adherence to diet and use of artificial sweeteners has been found. There is no evidence that artificial sweeteners are useful in wt control and reduction, except again for patients who have a craving for sweets. It is thought that saccharin use will not reduce dental caries, since 74% of all saccharin is used in beverages, usually sodas, which are not very carcinogenic because the sucrose is in soln. It was recommended that the polyalcohols mannitol, sorbitol, and xylitol, which are not cariogenic, be used as sweeteners rather than saccharin. The need for use of saccharin in patients with hyperlipidemia would be about the same as in diabetic patients. However, it may be of use in patients with hypoglycemia. Saccharin in drug formulations is useful because of its inertness, but its use should be re-evaluated on a drug-by-drug basis. (50 Refs)

320. SACCHARIN-SWEET AND DANGEROUS.
Mann GV
Vanderbilt Univ., Nashville, TN
Postgrad Med; 62(1):17-19 1977

The development of artificial sweeteners and the dangers of their use are discussed. The allegations that diabetics must avoid sugar and that artificial sweeteners are effective in the treatment of obesity are considered incorrect by the author. (4 Refs)

321. RELATIVE RISKS OF SACCHARIN AND CALORIE INGESTION.
Cohen BL
Dept. Physics and Astronomy, Univ. Pittsburgh, Pittsburgh, PA, 15260
Science; 199(4332):983 1978

A comparison was developed between the relative risks of saccharin and calorie intake. Previous studies have shown a risk of 1,200 bladder cancers per 6 x 10^7 drinks of diet soft drink. Since there is ordinarily a time delay of 10-50 yr between ingestion of a carcinogen and development of cancer, an av case would result in no more than a 20-yr loss of life expectancy. Thus an av diet drink would reduce life expectancy by 20 yr per 6 x 10^7 or approx 9 sec. The benefit of diet soft drinks result from their use in wt control by reducing caloric intake. The risk of ingesting one diet soft drink, which would cause a decrease in life expectancy of 9 sec, is approx equal to the risk of ingesting one additional kcal. If ingesting one diet drink inhibits ingestion of more than 1 kcal, its benefits exceed its risks. (7 Refs)

322. DO NON-CALORIC SWEETENERS AID PATIENTS WITH DIABETES TO ADHERE TO THEIR DIETS?
Farkas CS, Forbes CE
J Am Diet Assoc; 46:482-484 1965

323. SUCROSE SOLUTION VS. NONCALORIC SWEETENER VS. WATER IN WEIGHT GAIN.
Friedhoff R, Simon J, Friedhoff A
J Am Diet Assoc; 59:485 1971

324. EDUCATION AND MOTIVATION IN THE TREATMENT OF OBESITY.
Glenn MB
Am Coll Health Assoc J; 13:521-531 1964

325. DENTAL PLAQUE, DENTAL CARIES AND SUGAR INTAKE. THE EFFECTS ON THE PLAQUE OF A LOW-CALORIE SWEETENER USED IN BEVERAGES IN PLACE OF ORDINARY SUGAR.
Grenby TH
Br Dent J; 139:129-134 1975

326. SPECIALLY DESIGNED SWEETENERS AND FOOD FOR DIABETICS - A REAL NEED?
Lenner RA
Am J Clin Nutr; 29:726-733 1976

327. PHYSIOLOGICAL EFFECTS OF SUCROSE SUBSTITUTES AND ARTIFICIAL SWEETENERS ON GROWTH PATTERN AND ACID PRODUCTION OF GLUCOSE-GROWN STREPTOCOCCUS MUTANS STRAINS IN VITRO.
Linke HAB, Chang CA
Z Naturforsch; 31:245-251 1976

328. NON-CALORIC SWEETENER AND WEIGHT REDUCTION.
McCann MB, Trulson MF, Stulb SC
J Am Diet Assoc; 32:327-330 1956

329. EFFECT OF CONVERT NUTRITIVE DILUTION ON THE SPONTANEOUS FOOD INTAKE OF OBESE INDIVIDUALS: A PILOT STUDY.
Porikos KP, Booth G, Van Itallie T
Am J Clin Nutr; 30:1638-1644 1977

330. THE NEED FOR SPECIAL INDIVIDUALS WITH DIABETES MELLITUS.

Talbot JM

Life Sciences Research Office, Federation of American Societies for Experimental Biology. Prepared for the Bureau of Foods, Food and Drug Administration, U.S. Department of Health, Education and Welfare, Bethesda, MD, pp. 51, 1978.

331. POSITION STATEMENT ON SACCHARIN.

American Diabetes Association

Position Statement on Saccharin. American Diabetes Assoc., pp. 44, 1978.

IX. DEBATE CONCERNING GOVERNMENTAL REGULATION OF ARTIFICIAL SWEETENERS

332. PROPOSED SACCHARIN BAN STIRS UP CONGRESS.

Murray C

C and EN Washington

Chem Eng News; 55(13):22-23 1977

The Food and Drug Administration (FDA) announced that it has started proceedings to ban saccharin. The decision was based on a study sponsored by the Canadian government which "unequivocally" demonstrated that saccharin is a carcinogen: rats were fed 5% of the artificial sweetner in their food (the equivalent of eight 12 ounce diet drinks/day for humans) for two generations. Both parents and offspring developed significant numbers of kidney tumors; tumor incidence was higher in offspring. Several proposals have been put forth in Congress to modify the Delaney act, upon which the ban is based. Several epidemiologic studies of long-term saccharin users, particularly diabetics, have not shown any relation between use and bladder cancer. The acting director of NCI stated that human data does not convince NCI that saccharin is a carcinogen for humans. The FDA has four options concerning the saccharin ban and the Delaney act in general: to leave the Delaney amendment intact; to repeal the amendment and let the FDA regulate food additives under its general authority; to let the FDA permit use of additives in food that are carcinogenic in animals but pose no risk to humans at realistic levels of use; and to give the FDA authority to weigh the risks and benefits of a food additive. (no refs)

333. BITTER PILL FOR THE SWEET TOOTH.

Anonymous

No affiliation given

Med World News ; 18(7):10 1977

The Food and Drug Administration (FDA) ban of saccharin is discussed. The controversial Delaney clause, which says that the FDA must ban from the market any food additive found to cause cancer in people or animals, mandated the ban. The ban was based on a Canadian study showing that 3/100 rats maintained on diets of 5% saccharin developed malignant bladder tumors. Fourteen of 100 offspring also developed tumors. No evidence indicating that saccharin causes cancer in people has been found. Some members of Congress are trying to nullify the Delaney clause by legislation. Canadian authorities have solved the problem by making saccharin a behind-the-counter drug sold only in drug stores. (no refs)

334. CANCER TESTING TECHNOLOGY AND SACCHARIN.

Office of Technology Assessment

Office of Technology Assessment, Washington, DC

Cancer Testing Technology and Saccharin. Available from National Technical Information Service as Document Number PB-273 499/4GA., OTA-H-55, 143 pp., 1977.

The study was performed as part of the evaluation by the Congress of the proposed ban on saccharin by the Food and Drug Administration. The debate over cancer testing technology, saccharin use, and government regulation is introduced. The report (1) assesses the capacity of current testing methodology to predict the carcinogenic potential of chemicals, (2) evaluates the potential risk that saccharin consumption might cause cancer in humans, (3) evaluates the potential health benefits of saccharin, and (4) assesses the potential availability of alternative artificial sweeteners. Results of short term tests commissioned by the Office of Toxic Substances as part of the study are also reported. This assessment was performed in response to a request from the Committee on Human Resources of the US Senate. (Author abstract)

335. THE SACCHARIN DEBATE: REGULATION AND THE PUBLIC TASTE.

Lepkowski W

No affiliation given

Hastings Cent Rep; 7(6):5-7 1977

The political, economical, scientific and ethical issues concerning the proposed banning of saccharin are discussed. In the long run, education of the public is the most crucial aspect of saccharin control. Since saccharin is carcinogenic and it is of no use in wt control and the management of diabetes, its benefits (if any) must be determined. The efforts to ban saccharin in the early 1900's are reviewed. (no Refs)

336. REGULATING CARCINOGENS - THE BITTER AND THE SWEET.

Baldwin RH

Chemicals Div., Sherwin-Williams Co., 1370 Ontario St., Cleveland, OH, 44113

Chemtech; 9(3):156-162 1979

The 'one molecule' and 'threshold level' hypotheses for chemical carcinogenesis are described and discussed in light of the controversy surrounding the regulation of saccharin. The threshold hypothesis is thought to hold more promise as an approach to chemical carcinogenesis than the one-molecule hypothesis. The political implications of regulation, particularly when based on a lack of knowledge about the true effects of the chemical in question, are considered. A plea is made for a more liberal interpretation of the 'safe' quality of carcinogens. (16 Refs)

337. SACCHARIN - THE BITTER SWEET.

Isselbacher KJ, Cole P

Harvard Medical Sch., Boston, MA 02115

N Engl J Med; 296(23):1348-1350 1977

Arguments are presented against banning the use of saccharin. Recent studies have not shown the carcinogenic properties of saccharin in humans. It is recommended that legislation be changed to guard against inappropriate extrapolation to man of experimental evidence from other species, and to permit a balancing of the benefits of a food additive against its dangers. (14 Refs)

338. DELANEY CLAUSE DEBATE.
Jacin H, Stewart CA, Volkmann EW
Norwalk, CT
Chem Eng News; 55(31):3,30-31 1977

Dr. Jacin decries the lack of dose-response data in any of the published work implicating saccharin as a carcinogen. He states that the Food and Drug Administration study, the Wisconsin Alumni Research Foundation study and the Canadian study all presented data with no mention of dose response. Dr. Jacin goes on to point out that the Canadian study only indicated one metastasis and no invasiveness in any of the tumors found even though one criterion for the identification of cancer tumors is tissue invasion and metastasis. He feels that banning saccharin is a mistake. Stewart addresses himself to the variety of cancer causing agents and their effects at different dosages. He takes exception to the statement in the Delaney clause stating that if a substance does not produce cancer under the most extreme conditions it can be considered safe. Stewart states that, with the exception of smoking-related disease, the amount of cancer correlated with avoidable contaminants is very small. Volkmann states that, of the various epidemiological studies done on the incidence of colonic cancer, all implicate dietary factors as the causative agents and not specific synthetic chemicals. He feels that a balance should be struck between concern for dietary, emotional and chemical causative agents in the search for a cure. He feels that the more emphasis one places on dietary aspects as the causative agents and the less on chemicals, the less justification remains for the retention of the Delaney clause. (no Refs)

339. SOUR GRAPES OVER SACCHARIN (LETTER TO EDITOR).
Buchanan-Davidson DJ
Wisconsin Clinical Cancer Center, Madison, WI
Wis Med J; 76(10):18 1977

The controversy over the proposed ban on saccharin is discussed with relevant experimental studies reviewed. The risks of continued use of saccharin must be considered in light of the benefits of its use. Since all products containing saccharin must list it on the label, individuals can avoid its use.

340. SAVE DELANEY CLAUSE (LETTER TO EDITOR).
Brown KL
Univ. Texas, Arlington, TX
Chem Eng News; 55(34):58 1977

In connection with a forum on the Delaney amendment published in a recent issue of the Journal, the writer feels that the controversy over saccharin may lead to its repeal or amendment. The Delaney amendment should be preserved if only to raise the red flag of concern about the safety and effectiveness of individual food additives. (no Refs)

341. SAVE DELANEY CLAUSE (LETTER TO EDITOR).
Weinhouse S
Fels Res. Inst., Temple Univ., Philadelphia, PA.
Chem Eng News; 55(34):49,58 1977

Comments are presented on the opinions of various contributors to a recent forum on the Delaney clause published in the Journal. Earlier views on the safety of compounds based on acute toxicity tests plus a 'safety factor' are of limited value in terms of the time carcinogens may take to react. The safety of saccharin is also commented upon as is the operation of the Delaney clause. (no Refs)

342. SACCHARIN: THE PROBLEM OF SUCROSE SUBSTITUTES.
Rubin L, Price JH
Univ. Toledo, Toledo, OH
J Nursing Care; 12(8):16-22 1979

The chain of events leading to the ban of cyclamates and to the proposed ban of saccharin is summarized, and the controversy concerning the health effects of saccharin are discussed. Since conclusive carcinogenicity has not been determined, a review of some recommended actions and possibilities is presented. Personal decisions must be made by weighing the inherent risks and benefits of the use of saccharin. (32 Refs)

343. SACCHARIN: THE PROBLEM WITH SUCROSE SUBSTITUTES.
Felice PR
Dept. Pharmacology, West Virginia Univ. Medical Center, Morgantown, WV, 26506
J Sch Health; 49(5):284-285 1979

Aspects of the current controversy on the use of saccharin as a food additive are reviewed. A dose of 300 mg/day was considered safe for adults when saccharin was first evaluated 70 yr ago. A recent study suggested a possible relationship between saccharin intake and bladder tumors in rats and mice; simultaneously, a 6-yr chronic toxicity study failed to reveal any such relationship in rhesus monkeys. Saccharin is water soluble and is excreted essentially unchanged in the urine and feces. There is no evidence for the inherent toxicity of the two known metabolites of saccharin (o-sulfamoylbenzoic acid and ammonium-o-carboxybenzene), but the mutagenicity of saccharin bacterial systems has been demonstrated. No relationship between above av saccharin intake and bladder cancer could be demonstrated in patients with diabetes. Two natural sweeteners currently being tested might present alternatives to cyclamates and saccharin: aspartamine, an amino-acid like substance, and monellin, a proteinous sweetener isolated from Dioscoreophyllum cumminsii. (21 Refs)

344. SACCHARIN AND AFLATOXIN (LETTER TO EDITOR).
Jones JF
Cuyuga Falls, OH
FDA Consum; 11(8):5 1977

The action of the Food and Drug Administration in banning the use of saccharin is questioned, since aflatoxin is allowed to remain in some common foods. All carcinogens should be banned from our food supply. In the reply, it is noted that saccharin is an additive, while aflatoxin is an unavoidable contaminant, and the laws concerning such substances differ. (1 Refs)

345. MORE ON SACCHARIN (LETTER TO EDITOR).
Furth P
Los Angeles, CA
West J Med; 127(2):152 1977

In view of recent disclosures concerning bladder cancer caused by saccharin in man, physicians should support the Food and Drug Administration's decision to restrict its use. Carcinogenicity of other substances was proven in rats long before their effects were seen in man, and the same could be true for saccharin. (no Refs)

346. SACCHARIN EVIDENCE CRITICIZED (LETTER TO EDITOR).

Hancock JA
Norfolk, VA
FDA Consum; 11(6):6 1977

The Food and Drug Administration's ban on saccharin is unjustified because it lacks the epidemiological evidence of an increase in bladder cancer concurrent with, or subsequent to, the increased use of saccharin. A study on the incidence of bladder cancer among diabetics is suggested. (no Refs)

347. MONEY CAUSES CANCER: BAN IT (LETTER TO EDITOR).

Moore GE, Palmer WN
Denver General Hosp., Denver, CO
JAMA; 238(5):397 1977

Sarcomas developed in 9/35 rats within 14 mo of sterilized dimes being inserted into their peritoneal cavity thus proving that money causes cancer. The estimate is that malignant neoplasms will develop in more than 50% of the rats. It is suggested that, in the light of these results, all coins be banned from circulation. These experiments were done in response to recent Food and Drug Administration rulings to remove saccharin and other food additives from the market. (no Refs)

348. SACCHARIN: ITS PROHIBITION AND LIMITATION.

Borasi M, Meda GC
No affiliation given
Not Chim Farm; 17(2):40,42-44 1978

The carcinogenic potential of saccharin and its proposed ban by the US Food and Drug Administration is discussed. The action taken by Canada on this subject is also reviewed. (no Refs)

349. STUDY LINKS SACCHARIN TO CANCER IN HUMANS.

Author not identified
No affiliation given
FDA Consum; 11(6):3 1977

Various legal and scientific facts that form the basis for the proposed FDA ban on saccharin are reviewed. A Canadian study showed that men who consume saccharin are at a greater risk of developing bladder cancer. (no Refs)

350. CONSUMER REVOLT.

Jukes TH
No affiliation given
Nature (Lond); 266(5604):674 1977

The ban on saccharin proposed by the Food and Drug Administration, the result of a Canadian study, has unleashed intense public reaction. A human would have to drink 800 12-ounce cans of diet soda a day for a lifetime to ingest an amount of saccharin comparable to that received by rats in the Canadian study. Public rebuff of the Delaney Clause of the Federal Food and Cosmetic Act received support from eminent clinicians, who said they had seen practically no cases of bladder cancer in diabetics who had been on saccharin for many years. This implies that rats respond differently from human beings. It is hoped that opposition to banning saccharin will not jeopardize a program to reduce exposure to environmental carcinogens. (no refs)

351. CANCER SOCIETY TAKES PRO-SACCHARIN STAND.

Anonymous
No affiliation given
Science ; 196(4287):276 1977

The American Cancer Society has stated that saccharin is of great value in dietetic food. It is used to help control diabetes and obesity, which afflict tens of millions of people and pose more immediate dangers than the possible carcinogenicity of saccharin. Banning saccharin may cause great harm to many citizens while protecting a theoretical few. There is no evidence that saccharin causes cancer in humans. David Baltimore of the Massachusetts Institute of Technology challenged the statement. (no refs)

352. THE SACCHARIN QUESTION RE-EXAMINED: AN A.D.A. STATEMENT.

American Dietetic Association
430 N. Michigan Ave., Chicago, IL, 60611
J Am Diet Assoc; 74(1):574-581 1979

The regulatory processes applied to foods, existing information on the use of saccharin, the risk/benefit ratio, and alternatives to saccharin are reviewed. Saccharin has been identified as a potential carcinogen in some animal studies, and there is evidence that saccharin may promote the carcinogenicity of other substances. Determination of the risk rate in human populations is based on extrapolation of data from studies in which animals are exposed to high levels of a carcinogen. Epidemiologic studies to demonstrate the association between bladder cancer and saccharin intake in humans are inconclusive. There has been no objective documentation of the benefits of saccharin in diabetes, wt control, carbohydrate-restricted diets for treatment of hyperlipidemia, dental caries, or drug formulation. At the present time, saccharin is the only non-nutritive sweetener available in the United States; alternative nutritive sweeteners currently in use are xylitol, sorbitol, and fructose. (67 Refs)

353. FIGHT OVER PROPOSED SACCHARIN BAN WILL NOT BE SETTLED FOR MONTHS.

Culliton BJ
No affiliation given
Science ; 196(4287):276-278 1977

The Food and Drug Administration used "definitive" data indicting saccharin as a potential carcinogen to ban the sweetener. The Canadian study showed that saccharin, 5% of the total diet, caused an increased incidence of bladder cancer in rats; opponents of the ban say that a human would have to consume approx 800 12-ounce bottles of diet soda a day for life in order to consume a like amount. This argument obscures the experimental approach that, if a large dosage causes tumors in a significant number of animals during the course of their short lifetimes, a smaller dosage over a longer period can be expected to cause tumors in some people. The Canadian data also indicated that saccharin might be dangerous to unborn children. Congress has asked the Office of Technology Assessment to study the saccharin case. There is industrial pressure to allow cyclamates to be marketed again. Aspartame may be a future substitute for saccharin. (no refs)

354. ARE NITRITES AND SWEETENERS CARCINOGENIC?

Werko L
Astra AB, Sweden
Lakartidningen; 76(30/31):2607-2608 1979

The debates and controversies around saccharin and nitrite as food additives in the US are discussed. Saccharin was

found to be carcinogenic when administered to laboratory animals in very high doses, and nitrites have a tumor promoting rather than a carcinogenic effect. (5 Refs)

355. WHOSE VENTURE, WHOSE GAIN?

Anonymous
No affiliation given
Nature (Lond); 267(5614):741 1977

The acceptability of certain health risks in exchange for certain benefits is discussed. The ban on saccharin, the overuse of antibiotics and the increasing use of psychotropic drugs are considered. People are not rational about the acceptability of risks. They insist on being allowed to smoke, or to drive without seat belts, both of which carry large known hazards. They are also willing to accept the risk of disease to an unvaccinated child rather than the minuscule risk of damage by vaccination. (no Refs)

356. CANCER CONTROL: A BIGGER ROLE FOR GOVERNMENT.

Franklin BH
Consumer Product Safety Commission, Washington, DC
Chem Eng News; 56(3):34-37 1978

The background of the problem of regulating environmental carcinogens such as saccharin and Tris is presented. Federal involvement with the chemical industry and cancer research cuts across many agencies, making it difficult to develop a single, coherent policy. Open discussions on the causes and control of cancer are necessary to educate the public. Governmental policy should include the information necessary to regulate cancer-causing chemicals, the tests to be used, the interpretation of the results, and non-public health factors which should be considered. More government involvement is urged to produce a policy that spells out the magnitude of the problem and the need and action necessary for adequate consumer protection. The national policy should establish the framework, lay the ground rules, and coalesce the diverse concerns of the many federal agencies, industry, and the public. (no Refs)

357. SACCHARIN-A EUROPEAN ASSESSMENT (MEETING ABSTRACT).

Anonymous
no affiliation given
Food Cosmet Toxicol; 11(6):1126-1129 1973

Data available on the toxic and carcinogenic effects of saccharin were discussed. Of eight animal experiments, only two produced bladder tumors (in rats), but the experimental design of these studies should probably be considered as compromising features. The presence of o-toluenesulphonamide as a contaminant in some production batches of saccharin led to the recommendation that a limit be placed on its amount until the toxicological and carcinogenic potentials of this agent are examined. It was further suggested that final decisions concerning the use of saccharin be delayed until the results of epidemiological studies are available. Until that time it was recommended that certain limitations be placed on its use, including elimination of saccharin from baby food and products consumed largely by young children; restrictions on high saccharin intake by workers whose jobs favor dehydration and subsequently possible stone formation; and finally that the active ingredient be 5 mg/kg.

358. SACCHARIN BAN GOES BEYOND ISSUE OF CANCER.

Lepkowski WC
Chemical and Engineering News, Washington, DC
Chem Eng News; 55(15):17-21 1977

A review of all the research done on saccharin carcinogenesis showed that the substance increased the number of bladder tumors in at least six studies on rats, with cancer occurring in animals fed as little as 0.05% saccharin in the diet. Dietary doses as low as 0.01% (equivalent to 1.6 cans of dietary soda/day) resulted in an increase in leukemia, lymphomas, lymphosarcoma, and cancers of female reproductive organs. Since the excess cancer risk from saccharin is less than 30%, no epidemiological study can prove or disprove a cause-effect relationship. However, the larger issue surrounding the saccharin controversy is the role of sugars in the diet, especially sucrose and fructose. Animal studies show that these sugars cause large increases in blood trigylcerides, which have been identified as risk factors in heart disease and diabetes. Some researchers are concerned about the "metabolic overload" that high-sucrose and high-fructose diets may place on the body. Other researchers believe that the phenomenon of overload also applies to testing of chemical carcinogens. For example, 5 ppm of selenium (a required element) causes liver cancer in rats. (no refs)

359. CANCER RESEARCH TESTING (LETTER TO EDITOR).

Scribner JD
Pacific Northwest Res. Foundation, Seattle, WA
Chem Eng News; 55(41):62 1977

Experimental evidence is adduced to controvert the objections raised recently by a prominent scientist regarding the regulation of human exposure to potentially carcinogenic chemicals on the basis of animal tests. Even though detoxification as well as repair mechanisms exist in xenobiotics, repeated dose-response experiments with potent carcinogens lead to the conclusion that tumor initiators or complete carcinogens become more efficient at smaller doses. It has also been shown that not all lesions produced by chemical carcinogens are excised from target tissue DNA even after 1 mo. Since these chemicals cannot be very selective in damaging DNA, the most likely reason for the persistence of certain lesions is that they are not recognized by repair enzymes. Unless one is absolutely certain that a particular metabolite is necessary to cause cancer in animals and that the human system does not produce the same metabolite in any significant quantity, one is not morally justified to conclude that a particular chemical is not dangerous for humans. An important aspect of the saccharin/cyclamate story is that both of these compounds have been shown to cause bladder cancer (50% incidences) if given in the diet following a noncarcinogenic dose of the carcinogenic alkylating agent methylnitrosourea. Until one can establish a threshold dose for promoters, one cannot allow exposure to even potential promoters.

360. VALIDITY OF ANIMAL TESTING (LETTER TO EDITOR).

Cohn WE
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN 37830
Chem Eng News; 55(35):5 1977

The validity of animal tests that prove the carcinogenicity of saccharin in man is challenged. Animal tests apparently do not take into account detoxification mechanisms, repair mechanisms, and differences in metabolism between animals and man. (no Refs)

361. SACCHARIN, CANCER, AND CALORIES (2 LETTERS TO EDITOR).

Campbell TC
Federation American Societies Experimental Biology, Bethesda, MD, 20014
Science; 202(4365):260-262 1978

In comments on a report based on estimates of the Food and Drug Administration (FDA) linking bladder cancer to saccharin ingestion, species differences in response to

carcinogens are discussed. The responses can vary by three or four orders of magnitude. The assumption that noncaloric sweeteners reduce calorie consumption is also questioned. In reply, the FDA's risk estimate is also questioned and several examples of how uses of saccharin do decrease calorie intake are cited. (6 Refs)

362. PROPOSED CARCINOGEN POLICY (LETTER TO EDITOR).

White WI
No affiliation given
Chem Eng News; 56(3):51 1978

Three categories of carcinogens have been proposed by the Occupational Safety and Health Administration: one for carcinogens, one for suspected carcinogens and one for anything else. The disturbing aspect of the regulation is that there will be no distinguishing the potency of various carcingens. Thus, saccharin may have to be treated in the same manner as benzidine. Further comment on this subject is invited.

363. CYCLAMATE SWEETENERS.

Jukes TH
Univ. California, Space Sciences Lab., Berkeley, CA 94720
JAMA; 236(17):1987-1989 1976

In October of 1969, the Health, Education and Welfare Department removed the artificial sweetener cyclamate from the list of substances generally recognized as safe for use in food. The ban of the compound was based on an experiment which revealed papillary lesions in rats given high doses. Although the rats had received both cyclamate and saccharin (2,500 mg/kg body wt/day), cyclamate was blamed. The major effect of the ban on the public was psychological; the public had been constantly assured by the Food and Drug Administration (FDA), industry, and the National Academy of Sciences that cyclamates were safe. Reexamination and retesting did not confirm the results on which the ban was based. Although the FDA now considers it impossible to pinpoint cyclamate as the cause of positive tumorigenic response, it will not consider remarketing cyclamate for at least another 3 yr because of unresolved safety questions. (6 Refs)

364. CYCLAMATES: SCIENTIFIC DEMISE OR POLITICAL INTRIGUE? (PP. 1693-1708)

Thompson GR
International Flavors and Fragrances, Union Beach, NJ
Human Risk Assessment, Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation. Vol. 4, Hiatt HH, Watson JD, Winsten JA, ed. Cold Spring Harbor, Cold Spring Harbor Laboratory, Origins of Human Cancer., 1307-1889 pp., 1977.

Scientific and other factors that contributed to the Food and Drug Administration ban on cyclamates are reviewed. It is proposed that a regulatory decision should follow a two-step sequential procedure, the first step being scientific evaluation and judgment, and the second step, if necessary, social evaluation and judgment. (7 Refs)

365. CYCLAMATE: A TEST OF THE SYSTEM. (PP. 1683-1685)

Brown AL
Mayo Clinic, Rochester, MN, 55901
Human Risk Assessment, Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation. Vol. 4, Hiatt HH, Watson JD, Winsten JA, ed. Cold Spring Harbor, Cold Spring Harbor Laboratory, Origins of Human Cancer., 1307-1889 pp., 1977.

A brief history of the Food and Drug Administration ban on cyclamates is presented. Recent questions raised by the scrutiny of cyclamates, such as the precise definition of a carcinogen, the criteria that distinguish a benign tumor from a malignant one, and whether a compound once under suspicion can ever be accepted as noncarcinogenic, are discussed. (3 Refs)

366. CYCLAMATE AND ITS TOXICOLOGICAL ASPECTS.

Bruns VW, Engst R, Schramm T, Thymian E
Zentralinstitut fur Diabetes „Gerhardt Katsch" Karlsburg, Germany
Dtsch Gesundheitsw; 32(34):1585-1588 1977

Cyclamate belongs to those sweetening agents that are substances practically free of energy, disposing of an essential higher sweetening power than saccharose. The favorable qualities in its application and the non-objection in respect to health stated during 1940-1950 became the cause to apply it in dietetics in numerous countries in order to decrease overweight and moreover for the general application as an edulcorant for food in industry and household. Recent verifying results of examinations, however, led to a critical evaluation of this sweetening substance indicating a certain caution, causing the Ministry of Health to recommend cyclamate for diabetics and overweight persons only, but not for babies, infants, pregnant women and nursing mothers. (Author abstract) (33 Refs)

367. THE CYCLAMATE BAN.

Anonymous
No affiliation given
Lancet; 1(7974):1395 1976

The establishment of an acceptable daily intake limit to cyclamate would have permitted the study of its relationship to bladder tumors in humans without exposing them to testicular atrophy and raised blood pressure. However, since the ban is in effect, it will never be known if cyclamates are associated with bladder tumors.

368. REPORT ON CYCLAMATES BY THE COMMITTEE SET UP BY THE ISRAEL MINISTRY OF HEALTH.

Berenblum I
Weizmann Inst. Sci., Rehovot, Israel
Isr J Med Sci; 6(4):576-579 1970

Artificial sweetening agents, including saccharin and cyclamates, are consumed in Israel primarily in the form of tablets, "low calorie" syrups, and sugarless soft drinks, but their use is not as widespread as it has been in the United States. Studies of the carcinogenic properties of cyclamates in laboratory animals have shown that doses of cyclamates corresponding to a consumption of 3000 tablets/day for humans (2.5 g/kg body wt/day) produced tumors of the urinary bladder in rats; in addition, calcium cyclamate and cyclohexylamine have produced teratogenic effects when injected into chick embryos. Carcinogenic effects have not been demonstrated for cyclamates in man, and the doses which produce tumors in laboratory animals are 50 times the maximum conceivable dose that a man might take. Nevertheless, Israeli authorities have recommended the restriction of the use of cyclamate concentrates and syrups (but not of cyclamate tablets), and they have discouraged the use of any cyclamate-containing product during pregnancy.

369. CYCLAMATES AND FOOD SAFETY: AN FDA VIEW. (PP. 1687-1691)

Bates RR
Food and Drug Admin., Rockville, MD

Human Risk Assessment, Proceedings of the Cold Spring Harbor Conferences on Cell Proliferation. Vol. 4, Hiatt HH, Watson JD, Winsten JA, ed. Cold Spring Harbor, Cold Spring Harbor Laboratory, Origins of Human Cancer., 1307-1889 pp., 1977.

The cyclamate controversy is presented as an example of the general problem of how to deal with scientific uncertainty in the regulatory process. The discussion is limited to the problem of carcinogenicity. From the report of the NCI committee appointed to review the literature on cyclamates, it is clear that the committee members did not feel they were dealing with a carcinogen as potent as acetylaminofluorene. However, many phases in the report indicate real uncertainty as to whether the safety of cyclamate had been shown. These indications of uncertainty and concern expressed over the meaning of some of the experimental data indicate that the committee was not able to provide the level of assurance of safety to the American people that the Food and Drug Administration is expected to give with regard to the safety of food additives. Several quotations from the summary of the NCI committee report are discussed. Thus, from the committee's report the Commissioner of Food and Drugs was unable to conclude that the safety of cyclamates had been adequately demonstrated. (2 Refs)

370. TOXICOLOGICAL PROBLEMS OF IATROGENIC CARCINOGENESIS.

Schmahl D
German Cancer Res. Ctr., Heidelberg

Verh Dtsch Ges Pathol; 56:133-138 1972

It is recommended that long-term testing of drugs for carcinogenicity be restricted to: (1) agents suspected of being carcinogenic because of their constitution or chemical reactivity, e.g alkylating agents and (2) agents given to pregnant women and children at relatively large doses over long periods. These agents should be administered to at least two different species of carcinogen-sensitive animals for the life span of the animal. The difficulties of extrapolating results of animal tests to man are considered. Although alkylating agents may be of great value in cancer chemotherapy, they should not be used in other conditions in which the immunosuppressive action of corticosteroids or antimetabolites would suffice. Problems involved in taking potential carcinogens off the market are illustrated by using phenacetin, diethylstilbesterol, and cyclamates as examples.

371. CARCINOGENIC RISK OF PRODUCTS USED IN THE PHARMACEUTICAL AND RELATED INDUSTRIES.

Coustou F
Univ. Bordeaux II, Bordeaux, France

IARC Sci Publ; (25):129-149 1979

The problems, in France, of regulating drugs to eliminate or curtail potential carcinogenicity are reviewed. Some carcinogens may be introduced during the manufacturing process, such as asbestos during filtration, vinyl chloride in aerosol production or packaging, or 2-naphthylamine and other aniline compounds during the dyeing process. The use of artificial sweeteners in the manufacture of foodstuffs is banned in France. At present, general regulations of the French government for the pharmaceutical industry state that agents should be tested for carcinogenicity prior to marketing only if: (1) the agent is closely analogous to known carcinogens or cocarcinogens; (2) a suspicion of carcinogenicity has been aroused during long-term toxicological testing; (3) the drug is to be administered over long periods of time. (22 Refs)

372. CHEMICAL CARCINOGENS IN THE HUMAN ENVIRONMENT: PROBLEMS AND QUANTITATIVE ASPECTS.

Preussmann R
Deutsches Krebsforschungszentrum, Institut fur Toxikologie und Chemotherapie, Im Neuenheimer Feld 280, D-6900 Heidelberg, West Germany

Oncology; 33(2):51-57 1976

A review is given of the concept of environmental causation of human cancer. The problem of determining risk evaluations and preventive measures involves determination of a chemical's carcinogenicity and the monitoring and quantification of environmental carcinogens. Although some chemicals are clearly carcinogenic, others such as cyclamates are questionable. Currently environmental carcinogens are not being monitored regularly, partly because determination of trace quantities is analytically difficult and standardized reference methods have not been adopted. Problems that enter into quantification of environmental carcinogens and risk evaluation are discussed. Environmental levels of polycyclic aromatic hydrocarbons (PAH), aflatoxins, vinyl chloride (VC), and N-nitroso compounds are compared to the doses necessary to experimentally induce tumors. Exposure to PAH, the best representative of which is benz(a)pyrene (BP), is mainly via ingestion and inhalation. Among aflatoxins, which grow well in food products under certain conditions, aflatoxin B is the most potent hepatocarcinogen known. Occupational exposure to VC is causally connected with the induction of human angiosarcoma of the liver. Industrial discharge of VC and the use of PVC as a packaging material for food are sources of exposure of the general population. Several aspects of carcinogenic N-nitroso compounds are reviewed, including their content in food products. With the exception of aflatoxins, quantities of single carcinogens may be subthreshold. In view of syncarcinogenic and other enhancing and/or modifying effects, however, the probability of multifactorial cause of human cancer does not allow the definition of safe levels. (28 refs)

373. INTERNATIONAL ACTIVITIES IN THE FIELD OF FOOD ADDITIVES WITH PARTICULAR REFERENCE TO CARCINOGENICITY.

Lu FC
7452 SW 143 Ave., Miami, FL, 33183

Ecotoxicol Environ Saf; 3(3):301-309 1979

The regulations governing the use of food additives in the United States are compared with those of other countries and the recommendations of a joint committee established by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations. In addition, the historical development of the various regulations is summarized. Emphasis is placed on those regulations concerning cyclamates, saccharin, amaranth, and nitrites. Marked differences in regulatory decisions, especially between those of the United States and most other countries, can damage both public confidence in the soundness of the regulations and international food trade. Legislation as explicit as the Delaney Clause does not seem to exist in any country other than the United States. The Delaney Clause does not encourage flexibility regarding either the

interpretation of the soundness of the data or the weighing of the attendant risks and benefits. It therefore does not allow for value judgment, which may be essential in the assessment of the acceptability of a 'carcinogenic' food additive. (21 Refs)

374. EVALUATION OF ENVIRONMENTAL CARCINOGENS FOR CANCER IN MAN.

Brown AL
Mayo Clinic, Dept. Pathology and Anatomy, Rochester, MN 55902
Oncology; 33(2):58-60 1976

The responsibility of the scientific community is to identify chemical carcinogens in our environment and to determine safe or subthreshold levels to which these chemicals should be reduced. Regulatory decisions compounded of economic, social, and political factors and based upon sound scientific data are the responsibility of governmental agencies. The experimental design for testing possible carcinogens usually is a compromise between what is scientifically desirable and what is fiscally possible. Animal testing, or bioassay, has proved to be a useful technique for identification of carcinogens. However, the carcinogenicity or noncarcinogenicity of some chemicals, such as cyclamates, may never be known due to biological variability and the limits of sensitivity of currently available techniques. It is sometimes necessary to make regulatory decisions based on extrapolation from existing data, and it is the duty of the scientist to specify the limitations of experimental findings while working toward the development of more precise techniques. (5 refs)

375. CYCLAMATES AND SACCHARIN.

Swerdlow J
Abbott Lab. (Pty) Ltd., P. O. Box 1616, Johannesburg, S. Africa
S Afr Med J; 52(15):529-593 1977

A review of the experimental evidence which led to the banning of cyclamates is presented along with the consequences to the general public and especially diabetics of the removal of cyclamates and possibly saccharin from the food market. The safety of normal intake levels of both artificial sweeteners is stressed. The toxicity of very high doses of sugar (6 kg/day) is compared with high experimental doses of cyclamates (5 g/day). (no Refs)

376. STATEMENT TO THE SENATE COMMITTEE CONCERNED WITH FDA'S PROPOSED BAN OF SACCHARIN.

Nizel A
The Banning of Saccharin, 1977. Hearing Before the Subcommittee on Health and Scientific Research of the Committee on Human Resources. U.S. Senate, Ninety-fifth Congress, U.S. Government Printing Office, Washington, D.C., pp. 70-76, 1977.

377. SOME POSSIBLE RISK OF BANNING SACCHARIN.

Stunkard A
The Banning of Saccharin, 1977. Hearing Before the Subcommittee on Health and Scientific Research of the Committee on Human Resources. U.S. Senate, Ninety-fifth Congress, U.S. Government Printing Office, Washington, D.C., pp. 83-90, 1977.

X. REVIEWS

378. CARCINOGENICITY OF SACCHARIN.

Reuber MD
Chemical Carcinogenesis Program, NCI Frederick Cancer Res. Center, Frederick, MD, 21701
Environ Health Perspect; 25:173-200 1978

Published and unpublished carcinogenicity studies of saccharin are reviewed. Saccharin is carcinogenic for the urinary bladder in rats and mice, with male rats being more susceptible than females. Rats exposed as fetuses develop neoplasms more readily than rats exposed as weanlings. The lesions in the urinary bladder go through the stages of hyperplasia, hyperplastic nodules, and carcinomas. Neoplasms of the urinary bladder in rats were not caused by stones, parasites, sodium, or impurities. There is a cocarcinogenic effect between saccharin and methylnitrosourea for the urinary bladder. Chronic renal disease appears to result from low doses of saccharin, tumors of the renal pelvis and urinary bladder from higher doses. Benign and malignant neoplasms at all sites are increased significantly in mice and rats ingesting higher doses of saccharin. These neoplasms are present in the reproductive and hematopoietic systems and, to a lesser extent, in the lungs, vascular system, and squamous epithelium. Saccharin initiates skin neoplasms when its application is followed by croton oil. Three epidemiological studies reportedly show no increase in cancer of the urinary bladder following saccharin use. However, a Canadian study found an estimated 60% increase in cancer of the urinary bladder associated with the use of artifical sweeteners in men. (60 Refs)

379. IS THE USE OF SACCHARIN DANGEROUS?

Fossati C
Consorzio Provinciale Antitubercolare di Sondrio, Viale Italia, 41/15, 23037 Tirano, Italy
Clin Ter; 86(3):281-284 1978

A discussion of the literature on the carcinogenesis of saccharin is presented. Experiments using laboratory animals with short lifespans might not detect carcinogens that require a long period of use or a latency period. A study conducted by the United States Food and Drug Administration showed that cancer of the bladder increased 24% in male rats exposed to saccharin in utero. In England, no correlation was found between bladder cancer and the use of saccharin. In the author's experience with diabetics who used saccharin regularly, no evidence was found to indicate that it is carcinogenic. A study conducted by the Canadian Health Department showed that men who used saccharin had an incidence of bladder cancer 1.6 x greater than men who did not use it, and the incidence of cancer of the bladder increased with the frequency and duration of use. Both of these findings were statistically significant. In men, there probably is a correlation between the use of saccharin and cancer of the bladder. (13 Refs)

380. STATUS REPORT ON SACCHARIN IN HUMANS.

Newell GR, Hoover RN, Kolbye AC
NCI, NIH, Public Health Service, U. S. Dept. Health, Education, and Welfare, Bethesda, MD, 20014
J Natl Cancer Inst; 61(2):275-276 1978

A status report on the association between saccharin and bladder cancer in humans is presented. Background information is discussed, existing studies in humans are reviewed, and a proposed new study is described. In summary, there is not enough data to establish an association between the use of saccharin and an increased risk of bladder cancer in humans. (14 Refs)

381. ANTHRANILIC ACID. (PP. 265-275)
IARC Working Group
Lyon, France
IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Some Aromatic Amines and Related Nitro Compounds - Hair Dyes, Colouring Agents and Miscellaneous Industrial Chemicals. International Agency for Research on Cancer. Lyon, France, Vol. 16, 1978.

Carcinogenicity data on anthranilic acid, a compound used in the production of dyes and as a raw material in the manufacture of saccharin, were reviewed. This compound has been tested in mice by bladder implantation, but the data do not allow the carcinogenicity to be evaluated. A significant percentage of patients with nonoccupational bladder cancer excrete higher amounts of 3-hydroxyanthranilic acid than normal subjects, particularly after a loading dose of tryptophan, but no actual human carcinogenicity data were available for evaluation.

382. CONSIDERATIONS IN CHRONIC TOXICITY TESTING: THE CHEMICAL, THE DOSE, THE DESIGN.
Munro IC
Bureau Chemical Safety, Food Directorate, Health Protection Branch, Tunney's Pasture, Ottawa, Canada, KIA OL 2
J Environ Pathol Toxicol; 1(2):183-197 1977

Three areas involved in the planning of chronic toxicity tests, chemical purity, dose selection, and experimental design, are reviewed. Special attention must be given to potential impurities that may be responsible wholly or in part for the production of toxic effects. Potential impurities have been identified in saccharin and food colors. Prior to initiating chronic toxicity studies, the purity of the starting materials used in the manufacture of the test chemical should be assessed carefully, the manufacturing procedure should be reviewed to identify reactions that could produce impurities, and the stability of the test chemical during storage and in the diet or dosing vehicle should be determined. Before the selection of doses for carcinogen bioassays, the pharmacodynamic and, to the extent possible, metabolic behavior of the test compound should be examined to preclude the development of undesirable effects, apart from carcinogenesis, during bioassay. Whether or not bigenerational exposure is required to evaluate the carcinogenicity of the test substance will depend on its use pattern and pharmacokinetic and metabolic behavior in the mother and fetus. (23 Refs)

383. CAUSATIVE AGENTS IN THE INDUCTION OF BLADDER CANCER.
Jackson CD, Baetcke KP
Natl. Cancer Toxicological Res., Jefferson, AR 72079
Ann Clin Lab Sci; 6(3):223-232 1976

A survey of agents implicated in the tumorigenesis of human and animal bladder cancer is presented. Classes of compounds and individual compounds covered include aromatic amines (2-naphthylamine, benzidine, 4-aminodiphenyl, and phenacetin), nitrosamines (N-methyl-N'-nitro- N-nitrosoguanidine and N-nitroso-di-n-butylamine), natural products (cycasin and safrole), and sweeteners (saccharine and cyclamate). Epidemiological studies have implicated aromatic amines, widely used in the dye and rubber industries, in the development of bladder cancer, and in recent years the analgesic phenacetin has received attention as an etiologic factor. Safrole occurs in a number of species, and has given rise to experimental liver tumors in mice and rats. Cycasin, used in the tropics as a source of starch, produces tumors of liver, kidney, and lung in rats following long-term feeding. Bracken fern causes bovine bladder cancer. Further study is necessary to define the role of nitrosamines in the etiology of bladder cancer. Abnormal tryptophan metabolism has been implicated in a number of studies, but the role of this is currently unclear. Similarly, studies with saccharine and cyclamate are difficult to understand, and further work is necessary to clarify their possible roles.

384. NUTRITION AND CANCER: INGESTION OF FOODBORNE CARCINOGENS. (PP. 177-206)
Higginson J, Terracini B, Agthe C
Int. Agency for Res. on Cancer 150 Cours Albert Thomas, 69 Lyon 6cme France
Cancer Epidemiology and Prevention, Current Concepts. Schottenfeld D, ed. Springfield IL, Charles C Thomas, 1975

A review is presented of: (a) epidemiological evidence that suggests that cancers at specific sites (mouth, esophagus, stomach, colon and rectum, liver, pancreas, gallbladder and biliary passages, and genitourinary system) may be induced by particular dietary components; and (b) experimental evidence from animal studies indicating that certain dietary components are carcinogenic. Available carcinogenic data are given for food additives (food preservatives, such as nitrates and nitrites; food colors, such as auramine, magenta, amaranth, oil yellow OB and oil yellow AB, and carbon black; flavoring substances, such as safrole, isosafrole, cyclamates, and saccharin); possible contaminants (pesticides, including DDT, aldrin, dieldrin, chlorobenzilate, and mirex); feed additives, such as diethylstilbestrol; pollutants, such as polycyclic hydrocarbons, carcinogenic metals, and radioactive fallout; naturally occurring carcinogens such as the mycotoxin, aflatoxin B1 ; and certain intrinsic food components, such as cycasin, parasorbic acid, the pyrrolizidine alkaloids, and tannins, which are suspected carcinogens.

385. SACCHARIN: RISK AND BENEFITS.
Cohen BL
Nature (Lond); 271:492 1978

386. APPENDIX II. SHORT TERM TESTS.
McCann JC
Cancer Testing Technology and Saccharin Office of Technology Assessment, Congress U.S., Washington, D.C., pp. 91-144, 1977.

387. THE CURRENT STATUS OF SACCHARIN.
Munro I, Stavric B, Lacombe R
Toxicology Annual 1974. Winek A, ed. M. Dekker, Inc., New York, 1975.

388. SACCHARIN: TECHNICAL ASSESSMENT OF RISKS AND BENEFITS.
National Academy of Sciences
Saccharin: Technical Assessment of Risks and Benefits. National Academy of Sciences, Committee for a Study on Saccharin and Food Safety Policy. Washington, D.C., 1978.

389. SPECIFICATIONS FOR THE IDENTITY AND PURITY OF SOME FOOD COLOURS, FLAVOUR ENHANCERS, THICKENING AGENTS AND CERTAIN FOOD ADDITIVES.
Anonymous
Food Additive Series, No. 7. World Health Organization, pp. 203-205, 211-216, 1976.

390. SUMMARY OF TOXICOLOGICAL DATA OF CERTAIN FOOD ADDITIVES.

Anonymous

WHO Food Additive Series, No. 12. World Health Organization, 1977.

391. TOXICOLOGICAL EVALUATION OF SOME FLAVOURING SUBSTANCES AND NON-NUTRITIVE SWEETENING AGENTS.

Anonymous

WHO Food Additive Series 68.33. World Health Organization, pp. 82-99, 1967.

392. TOXICOLOGICAL EVALUATION OF SOME EXTRACTION SOLVENTS AND CERTAIN OTHER SUBSTANCES.

Anonymous

WHO Food Additive Series 70.39. World Health Organization, pp. 12-31, 1971.

393. EVALUATION OF CERTAIN FOOD ADDITIVES.

Anonymous

Twenty-first Report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series No. 617, 1978.

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